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(54) Title: INDOLE DERIVATIVES AND THEIR USES AS HEPARANASE INHIBITORS

(57) Abstract: The invention provides indole derivatives as heparanase inhibitors suitable for treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as cancer, inflammatory disorders and autoimmune diseases.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL02/00080

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/40, 31/405
US CL : 514/415, 416, 417, 418, 419

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/415, 416, 417, 418, 419

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, structural search, heparanase, antitumor, leukemia, anti-inflammatory, neoplasm, cardiovascular.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,262,403 A (NICOLSON et al) 16 November 1993, the entire document	1-26, 41-66, 81-106, 121-175
A	US 5,696,100 A (HOLME et al) 09 December, 1997, see the entire document.	1-26, 41-66, 81-106, 121-175.
A	US 5,919,809 A (EHRGOTT et al) 06 July 1999, see the entire document	1-26, 41-66, 81-106 and 121-175

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL02/00080

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claim Nos.: 27-40, 67-80, 107-120
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II. Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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INDOLE DERIVATIVES AND THEIR USES AS HEPARANASE INHIBITORS

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to heparanase inhibitors, particularly to certain indole derivatives, and to their use in the treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as cancer, inflammatory disorders and autoimmune diseases.

Heparan sulfate proteoglycans (HSPGs) are ubiquitous macromolecules associated with the cell surface and with the extracellular matrix (ECM) of various tissues. They consist of a protein core to which several linear heparan sulfate (HS) chains are covalently attached. Studies on the involvement of ECM molecules in cell attachment, growth and differentiation revealed a central role of HSPGs in embryonic morphogenesis, angiogenesis, neurite outgrowth, tissue repair, and metastasis. HSPGs are also prominent components of blood vessels. In capillaries they are found mainly in the subendothelial basement membrane, where they support proliferating and migrating endothelial cells and stabilize the structure of the capillary wall.

Several cellular enzymes such as collagenase IV, plasminogen activator, cathepsin B, and elastase are thought to be involved in the degradation of basement membrane. Another enzyme of this type is heparanase, an endo-β-D-glucuronidase that cleaves HS at specific intrachain sites (Nakajima et al., 1984). Heparanase released from cells removes HS molecules from the basement membrane resulting in increase of basement membrane permeability. Heparanase also facilitates proteolytic degradation of the core structural components such as type IV collagen in collaboration with gelatinases. Thus, blood-borne cells accomplish penetration through the basement membrane. In fact, HS catabolism is observed in wound repair, inflammation, and in diabetes.

Expression of heparanase was found to correlate with the metastatic potential of mouse lymphoma (Vlodavsky et al., 1983), fibrosarcoma and melanoma cells (Nakajima et al., 1988). Similar correlation was observed in human breast, colon, bladder, prostate, and liver carcinomas (Vlodavsky et al., 1999). Moreover, elevated levels of heparanase were detected in sera of metastatic tumor bearing animals (Nakajima et al., 1988) and of

cancer patients, in urine of highly metastatic patients (Vlodavsky et al., 1997), and in tumor biopsies (Vlodavsky et al., 1988). Treatment of experimental animals with heparanase substrates or inhibitors (e.g., non-anticoagulant species of low molecular weight heparin and polysulfated saccharides) considerably reduced the incidence of lung metastases induced by B16-F10 melanoma, pancreatic adenocarcinoma, Lewis lung carcinoma, and mammary adenocarcinoma cells (Vlodavsky et al., 1994; Nakajima et al., 1988; Parish et al., 1987; Lapierre et al., 1996), indicating that heparanase inhibitors may inhibit tumor cell invasion and metastasis.

Heparanase is involved also in primary tumor angiogenesis. Most primary solid tumors (1-2 mm diameter) obtain their oxygen and nutrient supply through a passive diffusion from pre-existing blood vessels, however the increase in their mass beyond this size requires angiogenesis. Heparin-binding polypeptides such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are highly mitogenic for vascular endothelial cells, and are among the most potent inducers of angiogenesis. bFGF has been extracted from the subendothelial ECM produced in vitro, and from basement membranes of cornea, suggesting that ECM may serve as a reservoir for bFGF. Immunohistochemical staining revealed the localization of bFGF in basement membranes of diverse tissues and blood vessels. bFGF binds to HSPG in the ECM and can be released in an active form by HS-degrading enzymes. Heparanase expressed by platelets, mast cells, neutrophils, and lymphoma cells was found to be involved in the release of active bFGF from ECM and basement membranes, suggesting that heparanase activity may not only function in cell migration and invasion, but may also elicit an indirect neovascular response (Elkin et al., 2001).

Heparanase catalytic activity correlates with the ability of activated cells of the immune system to leave the circulation and elicit both inflammatory and autoimmune responses. Interaction of platelets, granulocytes, T and B lymphocytes, macrophages, and mast cells with the subendothelial ECM is associated with degradation of HS by heparanase (Vlodavsky et al., 1992). The enzyme is released from intracellular compartments (e.g., lysosomes, specific granules) in response to various activation signals (e.g., thrombin, calcium ionophore, immune complexes, antigens, mitogens), suggesting its regulated involvement in inflammatory sites and in autoimmune diseases. Indeed, treatment of experimental animals with heparanase substrates (e.g., non-

anticoagulant species of low molecular weight heparin) markedly reduced the incidence of experimental autoimmune encephalomyelitis (EAE), adjuvant arthritis and graft rejection, indicating that heparanase inhibitors may inhibit autoimmune and inflammatory diseases (Lider et al., 1989).

Heparanase inhibitors have been proposed for treatment of human metastasis, for example, derivatives of siastatin B (Nishimura et al., 1994; Kawase et al., 1995), a pyran derivative isolated from the fungal strain *Acremonium* sp. MT70646 (PCT/KR00/01493), suramin, a polysulfonated naphthylurea (Nakajima et al., 1991), sulfated oligosaccharides, e.g., sulfated maltotetraose and maltohexaose (Parish et al., 1999), and sulfated polysaccharides (Parish et al., 1987; Lapierre et al., 1996).

U.S. Patent No. 5,968,822 discloses a polynucleotide encoding a polypeptide having heparanase catalytic activity and host cells, particularly insect cells, expressing said polypeptide. The recombinant polypeptide having heparanase activity is said to be useful for potential treatment of several diseases and disorders such as wound healing, angiogenesis, restenosis, inflammation and neurodegenerative diseases as well as for development of new drugs that inhibit tumor cell metastasis, inflammation and autoimmunity. International Patent Publication No. WO 99/57244 of the present applicants discloses bacterial, yeast and animal cells and methods for overexpressing recombinant heparanase in cellular systems. U.S. Patent No. 6,190,875, assigned to the present applicants, discloses methods of screening agents inhibiting heparanase catalytic activity and hence potentially inhibiting tumor metastasis, autoimmune and inflammatory diseases which comprises interacting a native or recombinant heparanase enzyme with a heparin substrate in the presence or absence of an agent and determining the inhibitory effect of said agent on the catalytic activity of said heparanase enzyme towards said heparin substrate. Both U.S. 5,968,822 and U.S. 6,190,875 and further WO 99/57244 are herein incorporated by reference in their entirety as if fully disclosed herein.

None of the above-mentioned publications and patents discloses or suggests the heparanase inhibitors of the present invention.

SUMMARY OF THE INVENTION

The present invention provides, in one aspect, a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one heparanase inhibitor selected from an indole derivative of the general Formula I or II hereinafter.

The pharmaceutical composition of the invention is particularly useful for the treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as, but not being limited to, cancer, inflammatory disorders and autoimmune diseases.

In another aspect, the present invention relates to the use of an indole derivative of the general Formula I or II for the manufacture of a pharmaceutical composition. In one embodiment, said compositions are for treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as, but not being limited to, cancer, inflammatory disorders and autoimmune diseases.

In a further aspect, the present invention provides certain novel indole derivatives of the general Formula I or II.

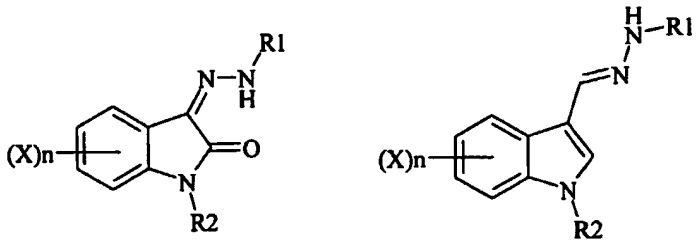
In still another aspect, the present invention relates to a method for treatment of a patient suffering from a disease or disorder caused by or associated with heparanase catalytic activity such as cancer, an inflammatory disorder or an autoimmune disease, which comprises administering to said patient an effective amount of an indole derivative of the general Formula I or II.

BRIEF DESCRIPTION OF THE FIGURES

Figs. 1A-B show transmigration rates through a Matrigel filter of mock-transfected (lacking heparanase) Eb murine lymphoma cells (Eb-cells) and *hepa*-transfected Eb murine lymphoma cells (Eb-heparanase cells) overexpressing heparanase, in the absence (-) or in the presence (+) of the chemoattractant SDF-1 (Fig. 1A), and of *hepa*-transfected Eb murine lymphoma cells (Eb-heparanase cells) overexpressing heparanase untreated (control) or treated with the compound herein identified as **Compound 4** (Fig. 1B).

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, pharmaceutical compositions are provided for treatment of diseases and disorders caused by or associated with heparanase catalytic activity, said compositions comprising a pharmaceutically acceptable carrier and at least one heparanase inhibitor which is an indole compound of the general Formula I or II:



(I) (II)

wherein

R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; or heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R2 is hydrogen; C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; said C6-C14 aryl or heteroaryl being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R3 and R4 each independently represents hydrogen, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

or R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

X represents halogen, nitro, -OR3, -SR3, -NR3R4, -SO_3H, –COOR3, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

n is an integer from 0 to 4;

and pharmaceutically acceptable salts thereof.

As used herein, the term "C1-C6 alkyl" typically refers to a straight or branched alkyl radical having 1-6 carbon atoms and includes for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-heptyl, 2,2-dimethylpropyl, n-hexyl and the like. Preferred alkyl groups are methyl, ethyl and propyl. The term "C2-C6 alkenyl" refers to straight or branched hydrocarbon radicals having 2-6 carbon atoms and one, preferably a terminal, double bond, and includes for example vinyl, prop-2-en-1-yl, but-3-en-1-yl, pent-4-en-1-yl, and hex-5-en-1-yl. Preferred alkenyl is prop-2-en-1-yl.

The terms "C1-C6 alkoxy" refers to the group C1-C6 alkyl-O-, wherein C1-C6 alkyl is as defined above. Examples of alkoxy are methoxy, ethoxy, hexoxy and the like.

The term "C6-C14 aryl" refers to an aromatic carbocyclic group having 6 to 14 carbon atoms consisting of a single ring or multiple condensed rings such as phenyl, naphthyl, and phenanthryl. The preferred aryl group is phenyl optionally substituted by C1-C6 alkyl, preferably methyl. The term "C7-C15 aroyl" refers to a group C6-C14 aryl-CO where aryl group is as defined above. Preferred aroyl groups are benzoyl and naphthoyl optionally substituted preferably by halogen, and/or by hydroxy and/or by a group NR3R4 wherein R3 is hydrogen and R4 is aroyl, preferably benzoyl.

The term "heteroaryl" refers to a monocyclic, bicyclic or tricyclic heteroaromatic group containing one to three heteroatoms selected from N, O and/or S such as, but not limited to, pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, quinolinyl, thiazolyl, pyrazolyl, quinazolinyl, 1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, indolyl, imidazo[1,2-a]pyridyl, benzimidazolyl, benzthiazolyl and benzoxazolyl. Preferred heteroaryl is quinolinyl optionally substituted by halogen, preferably chloro, and/or by hydroxy. It is to be understood that in a polycyclic heteroaromatic ring, the substituents may be in any of the heterorings and/or in any of the carbocyclic rings.

The term "halogen" refers to fluoro, chloro, bromo or iodo.

Preferred groups –NR3R4 are -NH_2, when R3 and R4 are both hydrogen, or R3 is hydrogen and R4 is a C7-C15 aroyl group as defined above.

Also contemplated by the present invention are pharmaceutically acceptable salts of the compounds of formula I or II.

Pharmaceutically acceptable salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S. M., et al., "Pharmaceutical Salts," (1977) J. of Pharmaceutical Science, 66:1-19). The salts can also be pharmaceutically acceptable quaternary salts such as a quaternary salt of the formula – NRR'R" + Z' wherein R, R' and R" each is independently hydrogen, alkyl or benzyl and Z is a counterion, including chloride, bromide, iodide, O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate.

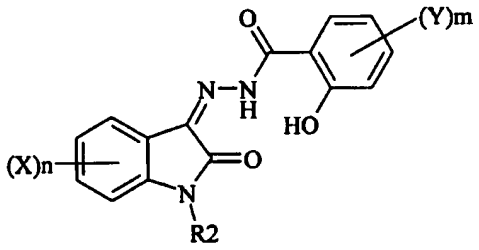
Pharmaceutically acceptable acid addition salts of the compounds include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as salts derived from organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate or galacturonate (see, for example, Berge S. M., et al., "Pharmaceutical Salts," (1977) J. of Pharmaceutical Science, 66:1-19).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms

differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

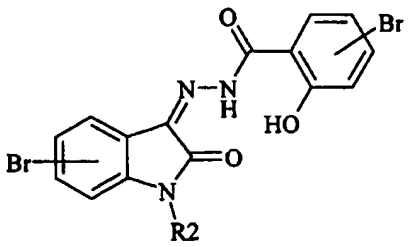
In one preferred embodiment of the invention, the pharmaceutical composition comprises a compound of the general Formula I, wherein R1 is C7-C15 aroyl, preferably benzoyl substituted by hydroxy at the ortho position and optionally further substituted by at least another radical Y, as depicted in formula Ia:



(Ia)

wherein Y is selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy, and X, R2, R3, R4 and n are as described hereinabove.

In a preferred embodiment, in the compound of formula Ia, m and n each is 1, X and Y are halogen, preferably Br, as depicted in formula Ib:

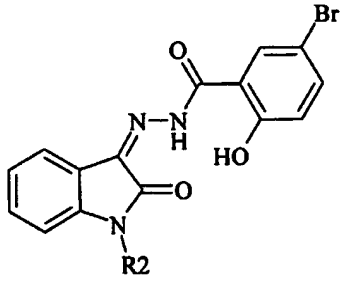


(Ib)

In the compound of formula Ib, when the Br at the indole ring is at position 5 and at the benzoyl group is para to the hydroxy group, and R2 is propyl, the compound is herein identified as **Compound 1** in the Appendix A just before the Claims. **Compound 1** is described in the literature [CAS No. 327026-31-3] but no biological activity is disclosed for the compound.

In another embodiment, when in the compound of formula Ib, the Br at the indole ring is at position 5 and at the benzoyl group is para to the hydroxy group, and R2 is prop-2-en-1-yl, the compound is herein identified as **Compound 2** in the Appendix A. **Compound 2** is described in the literature [CAS. 331247-87-8] but no biological activity is disclosed for the compound.

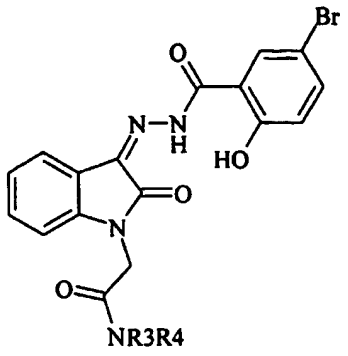
In a further embodiment of the present invention, the pharmaceutical composition comprises a compound of the formula Ia, wherein m is 1and Y is halogen, preferably Br at the para position to the hydroxy group; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; and n is 0, as depicted in the formula Ib':



(Ib')

In the compound of formula Ib', when R2 is benzyl, the compound is herein identified as **Compound 3** in the Appendix A. **Compound 3** is described in the literature [CAS No. 331247-83-3] but no biological activity is disclosed for it.

In yet another embodiment, the pharmaceutical composition comprises a compound of the formula Ic:

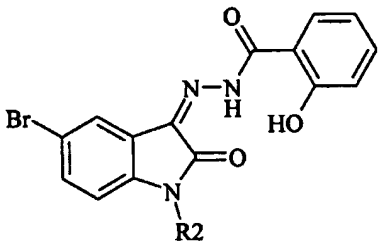


(Ic)

wherein R3 and R4 are as defined hereinabove.

In the compound of formula Ic, when R3 is hydrogen and R4 is phenyl substituted by a methyl group at position 4, the compound is herein identified as **Compound 4** in the Appendix A. **Compound 4** is described in the literature [CAS No. 322412-16-8] but no biological activity is disclosed for it.

In another preferred embodiment of the present invention, the pharmaceutical composition comprises a compound of the formula Ia, wherein n is 1, X is Br, and m is 0, as depicted in formula Id:

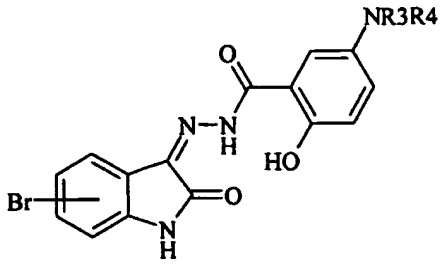


(Id)

In the formula Id, when R2 is benzyl, the compound is herein identified as **Compound 5** in the Appendix A. **Compound 5** is described in the literature [CAS No. 303016-40-2] but no biological activity is disclosed for it.

In yet another embodiment, the pharmaceutical composition comprises a compound of the formula Ia, wherein n is 2, X at position 5 is Br and at position 7 is methyl, and m is 0, as exemplified by the compound herein identified as **Compound 6** in the Appendix A. **Compound 6** is described in the literature [CAS No. 324023-09-8] but no biological activity is disclosed for this compound.

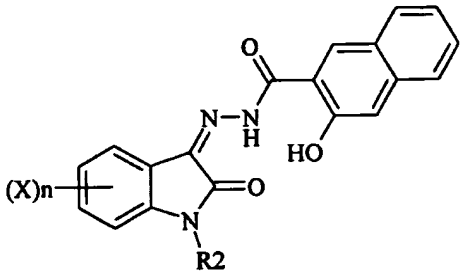
In a further embodiment of the present invention, the pharmaceutical composition comprises a compound of the formula Ia, wherein R2 is H, n is 1, X is Br and Y is –NR3R4 at the position para to the hydroxy group, as is depicted in formula Ie:



(Ie)

In the compound of formula Ie, when the Br is at the position 5, R3 is H and R4 is benzoyl, there is obtained the novel compound herein identified as **Compound 7** in the Appendix A.

In another preferred embodiment of the present invention, the pharmaceutical composition comprises a compound of the formula If:



(If)

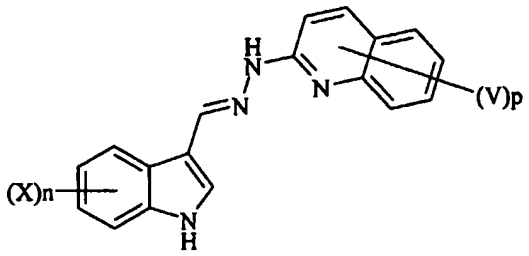
wherein X, R2 and n are as defined hereinabove.

In the compound of formula If, when R2 is hydrogen, n is 1 and X is F at the position 5, there is obtained the novel compound herein identified as **Compound 8** in the Appendix A just before the Claims.

In another preferred embodiment, in the compound of formula If, when n is 0 and R2 is propy-2-en-1-yl, there is obtained the compound herein identified as **Compound 9** in the Appendix A. **Compound 9** is described in the literature [CAS No. 322411-78-9] but no biological activity is disclosed for it.

In yet another preferred embodiment of the present invention, the pharmaceutical composition comprises a compound of the general Formula II, wherein R1 is heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three

heteroatoms selected from N, O and/or S, preferably quinolinyl, and being optionally substituted by at least one radical V, as depicted in formula IIa:



(IIa)

wherein V is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy, p is an integer from 0 to 6 and X, R3, R4 and n are as defined hereinabove. In one preferred embodiment, n is 0, p is 3 and V is Cl at positions 5 and 6 and hydroxy at position 8, as exemplified by the novel compound herein identified as **Compound 10** in the Appendix A.

The invention further relates to the novel **Compounds 7, 8** and **10.**

The indole **Compounds 1-9** may be prepared according to the general scheme depicted in **Scheme 1.** Thus, an appropriate derivative of 2-hydroxybenzoic acid methyl ester is reacted with an aqueous solution of hydrazine, obtaining the corresponding hydrazide derivative, that is then treated with the appropriate X, R2-substituted-indole-2,3-dione to afford the desired compound of formula Ia herein. Following this general procedure, **Compound 4** and the novel **Compounds 7** and **8** were prepared.

Compound 4 was prepared, as shown in **Scheme 2,** by reacting 5-bromo-2-hydroxybenzoic acid hydrazide with N-p-tolyl 2-(2,3-dioxo-2,3-dihydroindol-1-yl) acetamide in the presence of acetic acid.

Compound 7 was prepared according to the **Scheme 3,** by reacting N-(3-hydrazinocarbonyl-4-hydroxyphenyl)benzamide and 5-bromo-1H-indole-2,3-dione. **Compound 8** was similarly prepared by reacting 3-hydroxynaphthalene-2-carboxylic acid hydrazide and 5-fluoro-1H-indole-2,3-dione, as shown in **Scheme 4.**

Compound 10 was prepared, as shown in **Scheme 5,** from 5,6-dichloro-2-hydrazinoquinolin-8-ol and 1H-indole-3-carbaldehyde.

Although the procedures given are used specifically for the synthesis of the carbazole derivatives of this invention, the methods apply widely to analogous

compounds of Formula I and II, given appropriate consideration to protection and deprotection of reactive functional groups by methods standard to the art of Organic Chemistry. For example, in order to prevent unwanted side reactions, hydroxy groups generally need to be converted to ethers or esters during chemical reactions at other sites in the molecule. The hydroxy protecting group is readily removed to provide the free hydroxy group. Amino groups and carboxylic acid groups are similarly derivatized to protect then against unwanted side reactions. Typical protecting groups, and methods for attaching and cleaving them, are described fully by Greene and Wuts in Protective Groups in Organic Synthesis, John Wiley and Sons, New-York (2nd Ed, 1991) and McOmie, Protective Groups in Organic Chemistry, Plenum Press, New-York, 1973.

The inhibitory effect of the compounds of the present invention on heparanase activity can be evaluated by several methods carried out in vitro, ex vivo, or in vivo.

Some of the in vitro assays used according to the present invention were described in US 6,190,875. In these assays, heparanase is incubated with a heparanase substrate in the presence and in the absence of a compound of the present invention, and the inhibitory effect of the compound on the catalytic activity of the heparanase on its substrate is evaluated.

The heparanase may be natural mammalian heparanase, such as human heparanase purified as described in U.S. Patent 5,362,641 or, preferably, recombinant mammalian, e.g. human or mouse recombinant heparanase as described in US 5,968,822, US 6,190,875, and WO 99/57244, in purified or non-purified form. A source of non-purified recombinant heparanase is, for example, an extract of cells in which mammalian heparanase cDNA is expressed.

The heparanase substrate may be a natural heparan sulfate substrate, or an alternative substrate of the enzyme as described in U.S. 6,190,875, for example, heparin (e.g. heparin immobilized on a gel such as Sepharose), heparin fragments (e.g. several species of low molecular weight heparin), modified non-anticoagulant species of heparin, other sulfated polysaccharides (e.g. pentosan polysulfate), soluble HSPG or ECM.

Evaluation of the inhibitory effect can be carried out, for example, as described in US 6,190,875, by a size separation assay adapted for detection of degradation products of the heparanase substrate. Examples of such assays include gel electrophoresis and column chromatography.

Qualitative and quantitative evaluation of the catalytic activity of heparanase on its substrate and the inhibitory effect of a candidate inhibitor can be effected, for example, by colorimetric assays. Any colorimetric assay based on any color producing reaction is envisaged by the invention, be it a simple color reaction, which is readily detectable, or a fluorimetric or a luminiscent (e.g., chemiluminiscent) reaction, which are readily detectable by fluorescence detecting techniques. Examples of such suitable colorimetric assays include, but are not limited to, the dimethylmethylene blue (DMB), tetrazolium blue and carbazole assays. Qualitative colorimetric assays include the dimethylmethylene blue (DMB) assay, which yields color shift in the presence of polyanionic compounds such as sulfated glycosaminoglycans having different sizes that are released from the substrate (soluble or immobilized), and the carbazole assay, which detects uronic acid derivatives present in complete hydrolyzates of products released from an immobilized substrate, both assays being applicable for crude extracts of heparanase and for the purified enzyme as well.

In a preferred embodiment, a quantitative evaluation is desired and the preferred in vitro assays are those which are adapted for detection of reducing moieties associated with degradation products of the heparanase substrate, preferably a reducing sugar assay. An example of a quantitative colorimetric assay is the tetrazolium blue assay which allows colorimetric detection of reducing moieties released from the substrate, e.g. heparan sulfate, which may be present either in soluble or immobilized form.

Another possibility, although less preferred, consists in evaluating the catalytic activity of heparanase on the substrate by radioactive techniques, in which case the substrate used is radiolabeled, either in vitro or metabolically.

The ex vivo assays for evaluating the inhibitory effect of the compounds on heparanase activity include angiogenic sprout formation and transmigration assays. The angiogenic sprout formation assay is carried out in the rat aorta model (Nicosia et al., 1997; Nicosia and Ottinetti, 1990), whereby rat aorta rings are embedded in a basement membrane-like matrix composed of ECM-derived proteins such as laminin and collagen type IV, and HSPG, thus constituting a relevant heparanase substrate. The rings then develop angiogenic sprouts and angiogenesis can be quantitated. The compounds to be tested are added to the embedded aortic rings and their effect on angiogenic sprout formation is then evaluated.

In the ex vivo transwell migration assay, immune cell migration is evaluated, optionally in the presence of a chemoattractant factor such as stromal cell-derived factor 1 (SDF-1), a process which mimics in vivo extravasation of immune cells from the vasculature to sites of inflammation. In this assay, immune cells such as lymphocytes are let to migrate from the upper to the lower chamber through a transwell filter coated with a basement membrane-like matrix composed of ECM-derived proteins. The migration rate of the cells through the filter is then evaluated by counting the number of cells migrated through the filter (e.g. using a FACSort) compared to the number of cells added on top of the upper chamber. Over expression of heparanase in the immune cells results in an increase in the transmigration rate of the cells while addition of a heparanase inhibitor reduces the transmigration rate of the cells.

The inhibitory effect of the compounds on heparanase activity may be also assayed in vivo, for example, using the primary tumor growth or metastasis animal models or the sponge inflammation assay.

In the primary tumor animal model, animals are injected subcutaneously (s.c.) with tumor cells and treated with the heparanase inhibitors. Tumor growth is measured when animals in untreated control group start to die. For example, primary tumors may be generated with B16-F1 melanoma cells or with a highly metastatic subclone thereof injected s.c. into the flanks of mice. The mice are treated with heparanase inhibitors injected intraperitoneally (i.p.) twice a day starting 4 days after cell injection and are sacrificed and the tumor measured about 3 weeks after cell injection.

In the metastasis animal model, animals are injected intravenously (i.v.) with tumor cells and treated with the heparanase inhibitors. The number of lung metastasis is counted when animals in untreated control group start to die or about 3 weeks after cell injection. For example, metastasis may be generated with B16-F1 melanoma cells or with a highly metastatic subclone thereof injected i.v. to mice. The mice are treated with heparanase inhibitors injected i.p. at certain times following cell injection, and are then sacrificed and the number of lung metastasis is counted.

In the sponge inflammation assay, polyvinyl alcohol (PVA) sponges are implanted under the mouse skin and the mouse is kept untreated or is treated with a test inhibitor agent. One day later, the mouse is sacrificed, the sponges are taken out, squeezed into a tube and the number of cells in each sample is determined. After centrifugation, the

myeloperoxidase (MPO) content may be determined in a suspension of the cell pellets, and the TNF-α content in the supernatant of the sample. This assay mimics the inflammatory reaction resulting from the presence of a foreign body in the organism.

The heparanase inhibitors of the present invention can be used for the treatment of diseases and disorders caused by or associated with heparanase catalytic activity such as, but not limited to, cancer, inflammatory disorders and autoimmune diseases.

Thus, in one embodiment of the present invention, the compounds can be used for inhibition of angiogenesis, and are thus useful for the treatment of diseases and disorders associated with angiogenesis or neovascularization such as, but not limited to, tumor angiogenesis, ophthalmologic disorders such as diabetic retinipathy and macular degeneration, particularly age-related macular degeneration, reperfusion of gastric ulcer, and also for contraception or for inducing abortion at early stages of pregnancy.

In another embodiment of the invention, the compounds of general formulas I and II are useful for treatment or inhibition of a malignant cell proliferative disease or disorder.

According to this embodiment and due to the angiogenesis inhibitory activity of the compounds, they can be used for the treatment or inhibition of non-solid cancers, e.g hematopoietic malignancies such as all types of leukemia, e.g. acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), mast cell leukemia, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, Burkitt's lymphoma and multiple myeloma, as well as for the treatment or inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma.

It is to be understood that the compounds of the general formulas I and II are useful for treating or inhibiting tumors at all stages, namely tumor formation, primary tumors, tumor progression or tumor metastasis.

The compounds of general formulas I and II are also useful for inhibiting or treating other cell proliferative diseases or disorders such as psoriasis, hypertrophic scars, acne and sclerosis/scleroderma, and for inhibiting or treatment of other diseases or disorders such as polyps, multiple exostosis, hereditary exostosis, retrolental fibroplasia, hemangioma, and arteriovenous malformation.

In a further embodiment, the compounds of general formulas I and II are useful for treatment of or amelioration of inflammatory symptoms in any disease, condition or disorder where immune and/or inflammation suppression is beneficial such as, but not limited to, treatment of or amelioration of inflammatory symptoms in the joints, musculoskeletal and connective tissue disorders, or of inflammatory symptoms associated with hypersensitivity, allergic reactions, asthma, atherosclerosis, otitis and other otorhinolaryngological diseases, dermatitis and other skin diseases, posterior and anterior uveitis, conjunctivitis, optic neuritis, scleritis and other immune and/or inflammatory ophthalmic diseases.

In another preferred embodiment, the compounds of formulas I and II are useful for treatment of or amelioration of an autoimmune disease such as, but not limited to, Eaton-Lambert syndrome, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, autoimmune hemolytic anemia (AIHA), hepatitis, insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, plexus disorders e.g. acute brachial neuritis, polyglandular deficiency syndrome, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, thrombocytopenia, thyroiditis e.g. Hashimoto's disease, Sjögren's syndrome, allergic purpura, psoriasis, mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, polyarteritis nodosa, polymyalgia rheumatica, Wegener's granulomatosis, Reiter's syndrome, Behçet's syndrome, ankylosing spondylitis, pemphigus, bullous pemphigoid, dermatitis herpetiformis, Crohn's disease or autism.

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients. The carrier(s) must be acceptable in the sense that it is compatible

with the other ingredients of the composition and are not deleterious to the recipient thereof.

The term "carrier" refers to a diluent, adjuvant, excipient, or any other suitable vehicle. Such pharmaceutical carriers can be sterile liquids such as water and oils.

The pharmaceutical composition can be administered systemically, for example by parenteral, *e.g.* intravenous, intraperitoneal or intramuscular injection. In another example, the pharmaceutical composition can be introduced to a site by any suitable route including intravenous, subcutaneous, transcutaneous, topical, intramuscular, intraarticular, subconjunctival, or mucosal, *e.g.* oral, intranasal, or intraocular.

In one specific embodiment, the pharmaceutical composition is administered to the area in need of treatment. This may be achieved by, for example, local infusion during surgery, topical application, direct injection into the inflamed joint, directly onto the eye, etc.

For oral administration, the pharmaceutical preparation may be in liquid form, for example, solutions, syrups or suspensions, or in solid form as tablets, capsules and the like. For administration by inhalation, the compositions are conveniently delivered in the form of drops or aerosol sprays. For administration by injection, the formulations may be presented in unit dosage form, *e.g.* in ampoules or in multidose containers with an added preservative.

The compositions of the invention can also be delivered in a vesicle, in particular in liposomes. In another embodiment, the compositions can be delivered in a controlled release system.

The amount of the therapeutic or pharmaceutical composition of the invention which is effective in the treatment of a particular disease, condition or disorder will depend on the nature of the disease, condition or disorder and can be determined by standard clinical techniques. In general, the dosage ranges from about 0.01 mg/kg to about 50-100 mg/kg. In addition, in vitro assays as well in vivo experiments may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease, condition or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test

systems. For example, in order to obtain an effective mg/kg dose for humans based on data generated from mice or rat studies, the effective mg/kg dosage in mice or rats is divided by twelve or six, respectively.

The invention will now be illustrated by the following non-limiting examples.

EXAMPLES

For convenience and better understanding, the section of the Examples is divided into two subsections: (I) the Chemical Section describing the synthesis of the indole compounds, and (II) the Biological Section describing the biological activity of the compounds.

I CHEMICAL SECTION

The **Compounds 1-10**, which formulas are presented in Appendix A hereinafter, are identified in the Examples by their numbers in bold. The methods of preparation of the compounds are depicted in Appendix B as **Schemes 1-5**. The intermediates are identified in bold italics.

Materials

All reagents were purchased from Sigma-Aldrich Israel, Ltd., (Rehovot, Israel) and were used without further purification unless stated otherwise.

Compounds 1, 2, 3, 4, 5, 6, and **9** were purchased from ChemDiv, Chemical Diversity (San-Diego, CA, USA).

Example 1. General approach for the synthesis of Compounds 1-9

Compounds 1-9 may be prepared according to **Scheme 1**, by first reacting an appropriate derivative of 2-hydroxybenzoic acid methyl ester with an aqueous solution of hydrazine (step a). The product obtained, namely the Y-substituted-2-hydroxybenzoic acid hydrazide derivative, is then treated with an appropriate X, R2-substituted-indole-2,3-dione under acidic conditions to afford the desired X,Y,R2-substituted 2-hydroxybenzoic acid (2-oxo-1,2-dihydroindol-3-ylidene) hydrazide (step b).

Example 2. Synthesis of 2-{3-[(5-bromo-2-hydroxybenzoyl)hydrazono]-2-oxo-2,3-dihydroindol-1-yl}-N-p-tolylacetamide (Compound 4)

Compound 4 was prepared according to **Scheme 2**, by reacting 5-bromo-2-hydroxybenzoic acid hydrazide ***(intermediate ii)*** with 2-(2,3-dioxo-2,3-dihydroindol-1-yl) N-p-tolylacetamide ***(intermediate iv)***, as follows:

To a cold solution of 2-hydroxybenzoic acid methyl ester (10 g, 65.79 mmol) in 1,4-dioxane (250 mL) bromine (15 mL, 292.4 mmol) was added and the reaction mixture was left to react for 6 h at room temperature. Then, the solvent was removed under reduce pressure, thus obtaining ***intermediate i***. Next, to the solution of ***intermediate i*** in ethanol (200 mL), hydrazine monohydrate (10 mL, 206.4 mmol) was added dropwise and the reaction was allowed to stir overnight. The solvent was then removed under reduced pressure and the crude product was dissolved in CH_2Cl_2 (100 mL) and washed with water (30 mL x 3). The organic phase was separated, dried over sodium sulfate, filtered and evaporated under reduced pressure, thus obtaining ***intermediate ii***.

In a separate reaction, a solution of 4-aminotoluene (7 g, 65.42 mmol) in toluene (250 mL) was treated dropwise with chloroacetyl chloride (10mL, 125.5 mmol). The reaction was warmed to 65°C and was left to react for 4 hours. The reaction mixture was allowed to cool to room temperature, the solvent was evaporated under reduced pressure, thus obtaining ***intermediate iii***. To a cold solution of ***intermediate iii*** in DMF (100 mL), sodium hydride (2 g, 83.33 mmol) was added and the reaction mixture was left to react for 6 hours. Next, 1H-Indole-2,3-dione (10 g, 68.03 mmol) was added in one portion and the reaction mixture was allowed to react for 8 hours. The solvent was removed under reduced pressure, the solid was dissolved in toluene (100 mL) and washed with a brine

solution (30 mL x 3). The organic phase was removed under reduced pressure, thus obtaining ***intermediate iv***.

The crude ***intermediate ii*** and ***intermediate iv*** were dissolved in a mixture of ethanol (100 mL) and acetic acid (100 mL) and the solution was warmed at 50°C for 3 days. Then the solvent was removed under reduced pressure, thus obtaining a dark yellow solid identified as **Compound 4**.

^{1}H-NMR (DMSO-*d*6) ppm: 14.42 (s, 1H), 13.83 (s, 1H), 9.96 (s, 1H), 8.16 (s, 1H), 7.82 (d, 1H), 7.38(m, 4H), 7.19 (t, 1H), 7.02 (m, 3H), 6.82 (d, 1H), 4.48 (s, 2H), 2.21(s, 3H).

Example 3. Synthesis of N-[3-(5-bromo-2-oxo-1,2-dihydroindol-3-ylidene-hydrazino carbonyl)-4-hydroxyphenyl]benzamide (Compound 7)

Compound 7 was prepared by heating a mixture of N-(3-hydrazinocarbonyl-4-hydroxyphenyl) benzamide and 5-bromo-1H-indole-2,3-dione in a solvent mixture of ethanol and acetic acid, as shown in **Scheme 3**.

Example 4. Synthesis of 3-hydroxynaphthalene-2-carboxylic acid (5-fluoro-2-oxo-1,2-dihydroindol-3-ylidene) (Compound 8)

Compound 8 was prepared by heating a mixture of 3-hydroxynaphthalene-2-carboxylic acid hydrazide and 5-fluoro-1H-indole-2,3-dione in a solvent mixture of ethanol and acetic acid, as shown in **Scheme 4**.

Example 5. Synthesis of 5,6-dichloro-2-[N'-(1H-indol-3-ylmethylene)hydrazine] quinolin-8-ol (Compound 10)

Compound 10 was prepared, as shown in **Scheme 5**, by heating a mixture of 5,6-dichloro-2-hydrazinoquinolin-8-ol and 1H-indole-3-carbaldehyde in a solvent mixture of ethanol and acetic acid.

II BIOLOGICAL SECTION

Materials

Heparin Sepharose CL-6B was purchased from Pharmacia (Amersham Pharmacia Biotech) Uppsala, Sweden ; 1,9-Dimethylmethylene blue (DMB), tetrazolium blue and

heparan sulfate were purchased from Sigma-Aldrich (Rehovot, Israel); MCDB 131 medium was purchased from Clonetics (San Diego, CA, USA); DMEM and fetal calf serum were purchased from Gibco BRL (InVitrogen Corporation, CA, USA) ; glutamine and gentamicin were purchased from Biological Industries (Bet Haemek, Israel). Matrigel was kindly provided by Dr. H. Kleinmann, NIDR, NIH, Bethesda, MD, USA.

Methods

(a) In vitro Dimethylmethylene blue (DMB) assay for heparanase activity

Heparin Sepharose CL-6B beads were added up to the top of the wells of a multiscreen column loader (Millipore). A 96-well multiscreen plate containing 0.65 μm hydrophilic, low protein binding, Durapore membrane (Millipore) was placed, upside down, on top of the multiscreen column loader. The column loader and the multiscreen plate were held together, turned over, and the beads were uniformly transferred from the column loader to the multiscreen plate. Double-distilled water (DDW) was then added to the beads, which were allowed to swell for one minute, and then washed (three times) with DDW under vacuum. Heparin concentration was estimated to be 20 μM/well.

Human recombinant heparanase of at least 50% purity was obtained by expression in the CHO cells S1-11 subclone (generated as described for CHO clones S1PPT-4 and S1PPT-8 in WO 99/57244). Active human recombinant heparanase, purified from the CHO cell extracts by ion exchange chromatography (as described for the CHO 2TT1-8 subclone in WO 99/57244), was added (5 ng/well) to a reaction mixture containing 20 mM phosphate citrate buffer, pH 5.4, 1 mM $CaCl_2$, 1 mM NaCl, and 1 mM dithiothreitol (DTT; total volume of 100 μl). After 3-hour incubation at 37° C in a incubator on a vortex shaker, the heparanase reaction products were filtered under vacuum and collected into a 96-well polystyrene flat bottom plate (Greiner Cat. No. 655101). To each well, phosphate-buffered saline (PBS) containing 1% bovine serum albumin (BSA; 75 μl/well) and DMB (32 mg of DMB were dissolved in 5 ml ethanol, diluted to 1 liter with formate buffer containing 4 g sodium formate and 4 ml formic acid; 125 μl /well) were added. Color was developed after 5 minutes, and the absorbance of the samples was determined using a spectrophotometer (CECIL CE2040) at 530 nm. The absorbance correlated to heparanase activity. As a control, heparanase was added to the heparin Sepharose swollen

beads in the multiscreen plate and the heparanase reaction products were filtered immediately thereafter and the absorbance of these control samples was subtracted from all other samples.

Alternatively, instead of the partially purified human recombinant heparanase enzyme as above, crude extracts of CHO cells S1-11 subclone expressing human recombinant or crude extracts of CHO cells mhG9 clone expressing mouse recombinant heparanase (generated with the mouse heparanase cDNA as described for CHO clones expressing human recombinant heparanase in WO 99/57244) were used. The cell extracts were centrifuged and resuspended in 20 mM phosphate citrate buffer, pH 5.4 containing 50 mM NaCl. The cells were lysed by three cycles of freezing and thawing. The cell lysates were centrifuged (10000xg for 5 min), supernatants were collected and then assayed for heparanase activity using the DMB assay.

In order to examine whether a test compound exhibits an inhibitory effect on the heparanase activity, each compound was dissolved in dimethylsulfoxide (DMSO) and added, at a concentration range of 1-30 μM, to the heparin Sepharose swollen beads in the 96-multiscreen plate. The partially purified human recombinant heparanase or the crude cell extracts expressing either human or mouse recombinant heparanase was added for a 3-hour incubation and the reaction continued as described above. Color was developed and the absorbance was measured as described above. The IC_{50} value (the concentration at which the heparanase activity was inhibited by 50%) for each compound was evaluated.

(b) <u>In vitro tetrazolium blue assay for heparanase activity</u>

Human recombinant heparanase of at least 50% purity (obtained by expression in the CHO cells S1-11 subclone as described in (a) above) was added (4 ng) to each well of a 96-well microplate and incubated in a reaction mixture containing 20 mM phosphate citrate buffer, pH 5.4, 1 mM $CaCl_2$, 1 mM NaCl, and 4 μM heparan sulfate (final volume of 100 μl). After 3 hours of incubation at 37° C in an incubator on a vortex shaker, the reaction was stopped by the addition of tetrazolium blue reagent (0.11% tetrazolium blue in 0.1 M NaOH; 100 μl/well). Color was developed by incubation of the plates at 60°C for 2 hours. For each assay, a control reaction, which did not contain the substrate (heparan sulfate), was included. Color intensity was quantitatively determined in a

microplate reader (Dynatech) at 580 nm. Heparanase activity was calculated as the difference between the O.D of the sample containing the substrate, and the O.D. of the sample not containing the substrate. The background O.D. produced by the substrate was also subtracted from all the samples. The absorbance correlated to heparanase activity. The IC_{50} value (the concentration at which the heparanase activity was inhibited by 50%) for each compound was evaluated.

(c) Ex vivo angiogenic sprout formation assay for heparanase activity

As described in the Background section, previous studies have demonstrated the involvement of heparanase in angiogenesis. In order to test whether the heparanase inhibitors of the present invention can inhibit angiogenesis, the rat aorta model of angiogenesis as previously described (Nicosia et al., 1997; Nicosia and Ottinetti, 1990) was used with some modifications. In this model, the rat aortic endothelium exposed to a three-dimensional matrix of collagen or other ECM-derived proteins, switches to a microvascular phenotype, generating branching networks of microvessels. Angiogenesis is triggered by the injury caused by the dissection procedure and does not require stimulation by exogenous growth factors. Therefore, the rat aorta model can be used to investigate the endogenous mechanisms by which blood vessels regulate angiogenesis during wound healing.

Briefly, thoracic aortas were excised from 2- to 3-month-old Fischer 344 male rats, rinsed in serum-free MCDB 131 growth medium containing 50 μg/ml gentamicin, cleaned of periadventitial fibroadipose tissue, and cross-sectioned at ~1 mm intervals. Freshly cut aortic rings were rinsed in serum-free MCDB 131 medium and each ring was embedded in Matrigel (a basement membrane-like matrix composed of ECM-derived proteins such as laminin and collagen type IV and others, and HSPG, thus constituting a relevant heparanase substrate). Matrigel cultures were transferred to 18-mm wells of 4-well plates (Nunc) and grown at 35.5°C in 0.5 ml of serum-free MCDB131 medium that was changed 3 times a week. Angiogenesis was quantitated by counting the number of neovessels according to published criteria (Nicosia and Ottinetti, 1990). In order to examine the inhibitory effect, a test compound was added to the Matrigel aortic ring cultures and its effect on reduction of the number of new microvessels was determined in comparison with untreated cultures.

(d) <u>In vivo mouse melanoma primary tumor growth assay for heparanase activity</u>

Instead of using a primary tumor cell line, primary tumor was generated in C57BL mice by cells herein designated FOR cells, which were generated as follows: B16-F1 mouse melanoma cells (ATCC No. 6326) were grown in DMEM containing 10% fetal calf serum, 2 mM glutamine, and 50 μg/ml gentamicin. A subclone of the B16-F1 cell line, F1-J, produced large amounts of melanin and exhibited a highly metastasis potential. These highly metastatic F1-J cells were injected to syngeneic mice (100,000 cells, s.c.). Cells from metastases that were formed were cultured in different conditions. A clone, F1-LG, designated herein FOR, was selected by its high heparanase expression and activity using the reverse transcriptase-polymerase chain reaction (RT-PCR) and the radiolabeled ECM degradation analyses, respectively, as previously described (Vlodavsky et al., 1999; U.S. 6,190,875).

FOR cells were grown in DMEM containing 10% fetal calf serum, 2 mM glutamine, and 50 μg/ml gentamicin until they reached confluence (typically 4-5 days) and then splitted (1:5). This splitting yielded subconfluent and growing cells at day 7, the day of cell injection, at which the cells were trypsinized, washed with PBS and counted to yield a cell suspension of 10^6 cells/ml in PBS. Male C57BL mice (~20 gram each; at least 10 mice/group) were injected s.c. on the flank with a suspension of the FOR cells (100 μl/mouse). Four days later, a test compound dissolved in DMSO was injected (100 μl) i.p to the mice, twice a day (morning and evening). Each compound was injected at either 1 or 2 different concentrations (0.1 and/or 0.5 mg/mouse/day). Control mice were injected i.p. with DMSO only (100 μl). Mice were observed daily, and usually three weeks after cell injection, mice were sacrificed, the tumors were harvested and weighted.

(e) <u>In vivo mouse melanoma metastasis assay for heparanase activity</u>

FOR cells were cultured as described in (d) above. After trypsinization, the cells were washed with PBS and counted to yield a cell suspension of $1.5x10^6$ cells/ml in PBS. Male C57BL mice (~20 gram each; at least 10 mice/group) were injected i.v. with a suspension of the FOR cells (100 μl/mouse). A test compound dissolved in DMSO was injected (100 μl) i.p to the mice 4 and 8 hours after cell injection. The compound was injected at 1 or 2 different concentrations (0.5 and/or 1 mg/mouse/day). Control mice

were injected i.p. with DMSO only. Mice were observed daily, and three weeks after cell injecion, mice were sacrificed, the lungs were fixed in Bouen's solution and scored for the number of metastatic nodules as previously described (Vlodavsky et al., 1994).

(f) Transmigration assay for heparanase activity

An in vitro chamber-like transmigration system was established by using transwell filters coated with a reconstituted basement membrane-like matrix (Matrigel). Matrigel is was composed of laminin, collagen type IV, entactin and nidogen, as well as of HSPG, thus constituting a relevant heparanase substrate. The cells used in the experiment were mock-transfected Eb murine lymphoma cells not expressing heparanase and stable *hepa*-transfected Eb murine lymphoma cells overexpressing heparanase (both cells described by Vlodavsky et al., 1999). The migration rate of the cells trough Matrigel was evaluated first in the absence and in the presence of the chemoattractant SDF-1 without the heparanase inhibitors of the invention. Once the transmigration of the cells to the lower chamber was shown to be well correlated with the heparanase expression levels and activity, the transmigration of the Eb cells overexpressing heparanase was tested after treatment with the heparanase inhibitors of the invention. Addition of the heparanase inhibitor reduces the transmigration rate of the cells.

Example II (1). In vitro inhibition of heparanase activity by compounds of the invention

The inhibition of heparanase activity by the compounds of the present invention was first detected in two colorimetric in vitro assays, i.e., the DMB assay and the tetrazolium blue assay as described in Methods (a) and (b) above. The human recombinant heparanase (designated h-hepa) expressed in CHO cells S1-11 subclone was used herein either in its partially purified form (50% purity) or in crude cell extracts, and the mouse recombinant heparanase (designated m-hepa) expressed in CHO cells mhG9 was used herein in crude cell extracts only.

The results of the IC_{50} values of the different compounds are shown in Table 1. All the tested compounds were found to inhibit heparanase activity at micromolar concentrations. However, **Compounds 2, 4** and **10** were shown to be more potent than

the others in the DMB (h-hepa) assay with IC_{50} values in the range of 10.3-11 μM compared to IC_{50} values in the range of 17 to 26 μM for the other compounds.

Table 1. IC_{50} values of the tested compounds for inhibition of heparanase as detected by the in vitro DMB and tetrazolium assays.

Compound	DMB (h-hepa) IC_{50}[μM]	Tetrazolium (h-hepa) IC_{50}[μM]	DMB of cell extract (h-hepa) IC_{50}[μM]	DMB of cell extract (m-hepa) IC_{50}[μM]
1	18		106	28
2	11		44	16
3	19		43	23
4	11	35	52	28
5	17		92	39
6	17		81	46
7	17			
8	19		54	23
9	26			
10	10.3	20	45	52

Example II(2). Inhibition of mouse melanoma primary tumor growth and of metastasis by Compound 4

The effect of **Compound 4** on primary tumor growth and on metastasis was assayed as described in Methods (d) and (e) above. The results are summarized in Tables 2 and 3.

As shown in Table 2, untreated control mice developed primary tumors with an average weight of 0.1 g. Treatment with **Compound 4** (0.5 mg/mouse/day) significantly reduced the tumor size by a factor of 3 (average weight of 0.04 g).

The effect of **Compound 4** was further tested in melanoma metastasis as described in Method (e) above. The results, summarized in Table 3, show that the average number of metastatic nodules in the lungs of control, untreated mice was 13.5, while treatment with **Compound 4** at a daily dosage of 3.0 mg/mouse/day significantly reduced the lung metastatic nodules, now amounting to only 2.

Table 2. Effect of Compound 4 on mouse melanoma primary tumor growth

Dose [mg /mouse/day]		
Tumor weight (gr)	Control	0.5 mg/kg
	0.18	0.05
	0.34	0.1
	0.78	0.03
	0.1	0.02
	0.07	0.08
	1.04	0.02
	0.09	0.2
	0.01	0.06
	0	0
		0
Median	0.1	0.04
Range	0 - 1.04	0 - 0.10

Table 3. Effect of Compound 4 on mouse melanoma metastasis

Dose [mg/mouse/day]			
Number of metastasis	Control	3.0 mg/kg	1.0 mg/kg
	8	2	0
	15	2	10
	6	2	18
	0	2	50
	100	2	8
	50	5	0
	22	1	25
	12	10	0
	21	2	1
	2	3	18
	18		
	0		
Median	13.5	2	9
Range	0-100	1-10	0-50

Example II(3). Reduction of transmigration of Eb-heparanase cells by Compound 4

The effect of **Compound 4** on the transmigration of Eb murine lymphoma cells overexpressing heparanase (herein 'Eb-heparanase' cells) was assayed as described in Method (f) above. The results are summarized in Figs. 1A-B.

In the first experiment, transwell units (Costar, Cambridge, MA, USA) were coated with Matrigel (15 µl/well) and left for 8 hours at 37 °C to allow the gel to polymerize. Then, Eb murine T-lymphoma cells, either mock-transfected (lacking heparanase) or heparanase-transfected (overexpressing heparanase), were plated in the transwell units (200,000 cells/well). The chemoattractant SDF-1 (PeproTech, Rocky Hill, NJ, USA) was added (250 ng/ml) to the lower chamber of the transwell units and the cells were allowed to migrate for 16 hours. Transmigration was evaluated with the CellTiter kit according to the manufacturer's instructions (Promega, Madison, WI, USA). Results are presented as % of cells migrated to the lower chamber out of the total number of cells added to the transwell unit.

As shown in Fig. 1A, plating of the mock-transfected Eb murine lymphoma cells in the absence of SDF-1 resulted in transmigration of 1.5% of cells to the lower chamber, while plating of the stable heparanase-transfected Eb cells resulted in a 5-fold increase in the transmigration rate (7.4 %). Thus, transmigration magnitude was shown to nicely correlate with the heparanase expression levels and activity. Fig. 1A also shows that transmigration of the cells was further enhanced by the chemoattractant SDF-1: 5.3 % for the mock-transfected cells and 15.7 % for the heparanase-transfected Eb cells. A three-fold increase in the transmigration rate of the Eb-cells was noted as compared to the control, suggesting that heparanase also contributed to the transmigration potential of the cells.

Transmigration of the Eb-heparanase cells treated with **Compound 4** (200 µl of a 3 mg/ml solution of **Compound 4** were added to the cells in the upper chamber) was then tested. As shown in Fig. 1B, **Compound 4** reduced transmigration of the Eb-heparanase cells by about 30%.

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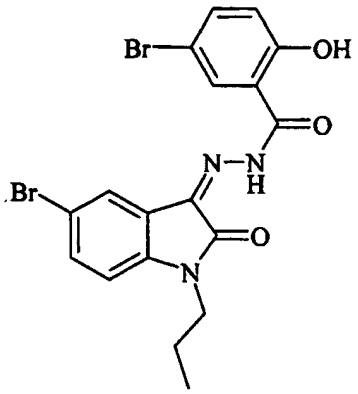
Appendix A- Compounds 1-10

Compound 1



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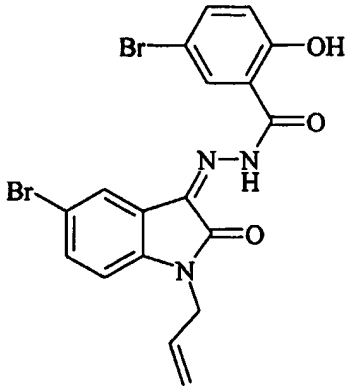

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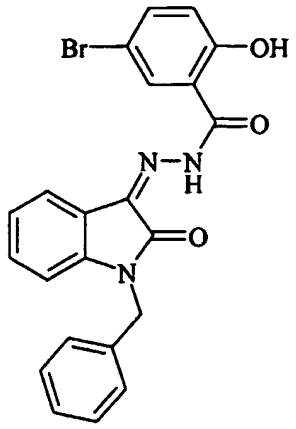

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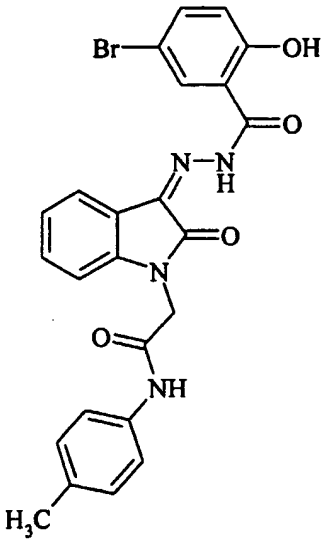

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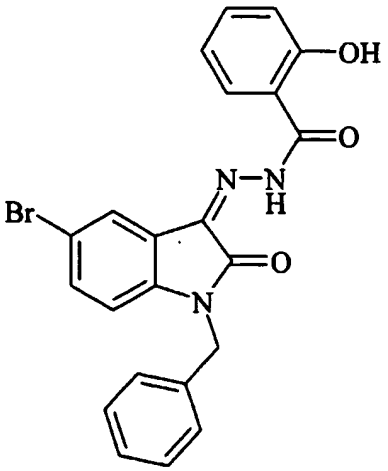

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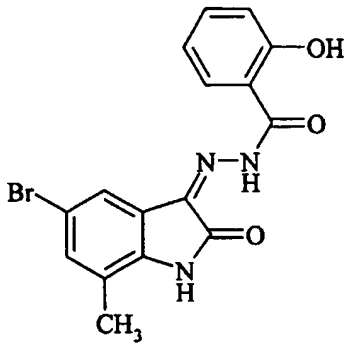

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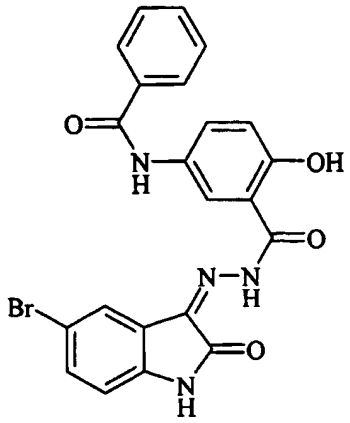
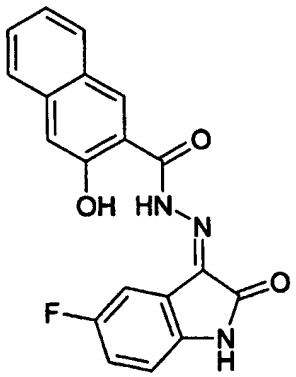


Compound 8



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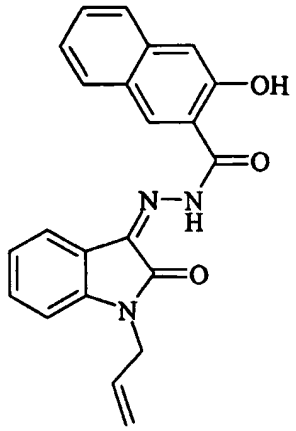
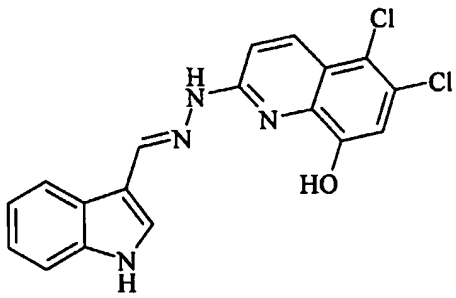
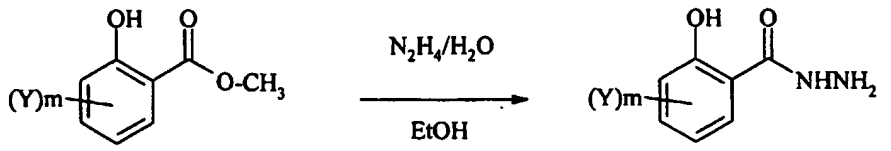


Compound 10

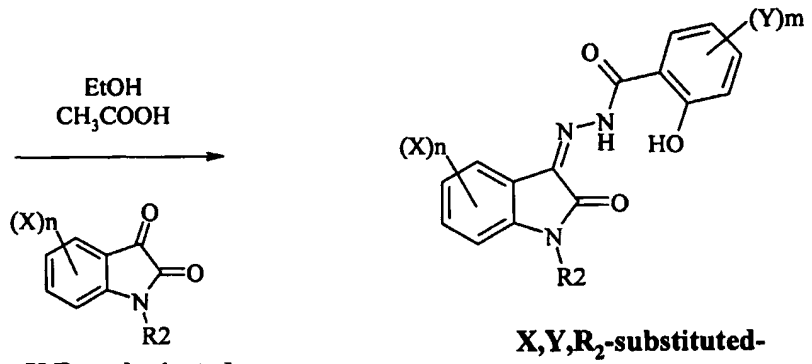


Appendix B-SCHEMES



Y-substituted-2-Hydroxy-benzoic acid methyl ester

Y-substituted-2-Hydroxy-benzoic acid hydrazide

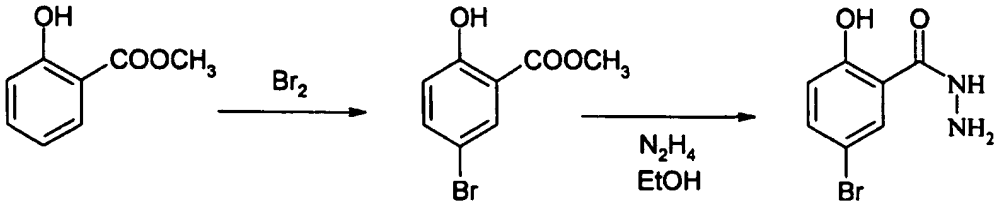


X,R_2-substituted-Indole-2,3-dione

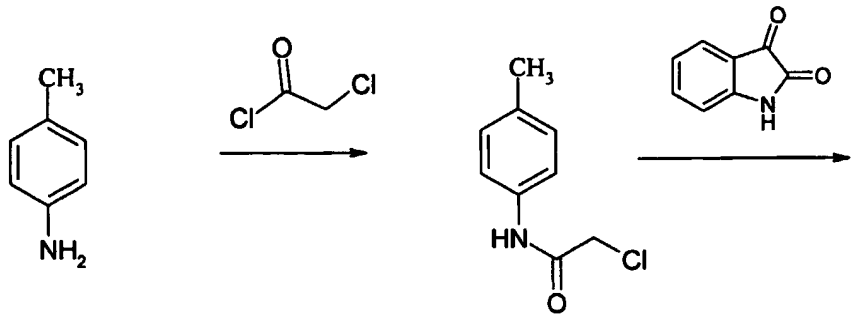
(step a)

X,Y,R_2-substituted-2-Hydroxybenzoic acid (2-oxo-1,2-dihydroindol-3-ylidene)hydrazide

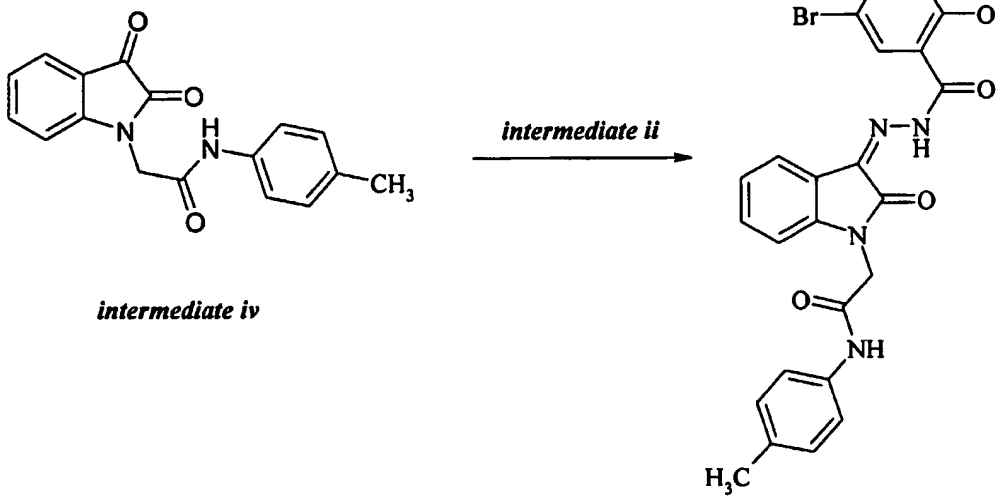
Scheme 1



intermediate i *intermediate ii*



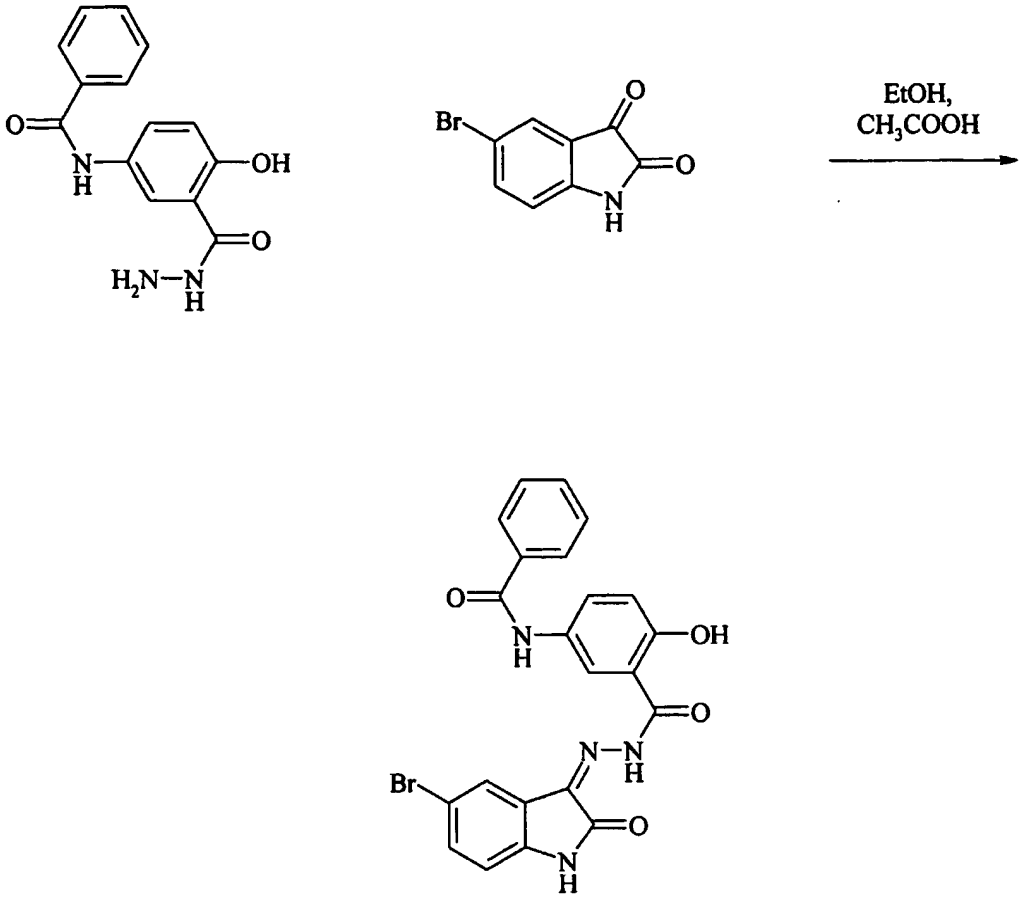
intermediate iii



intermediate iv

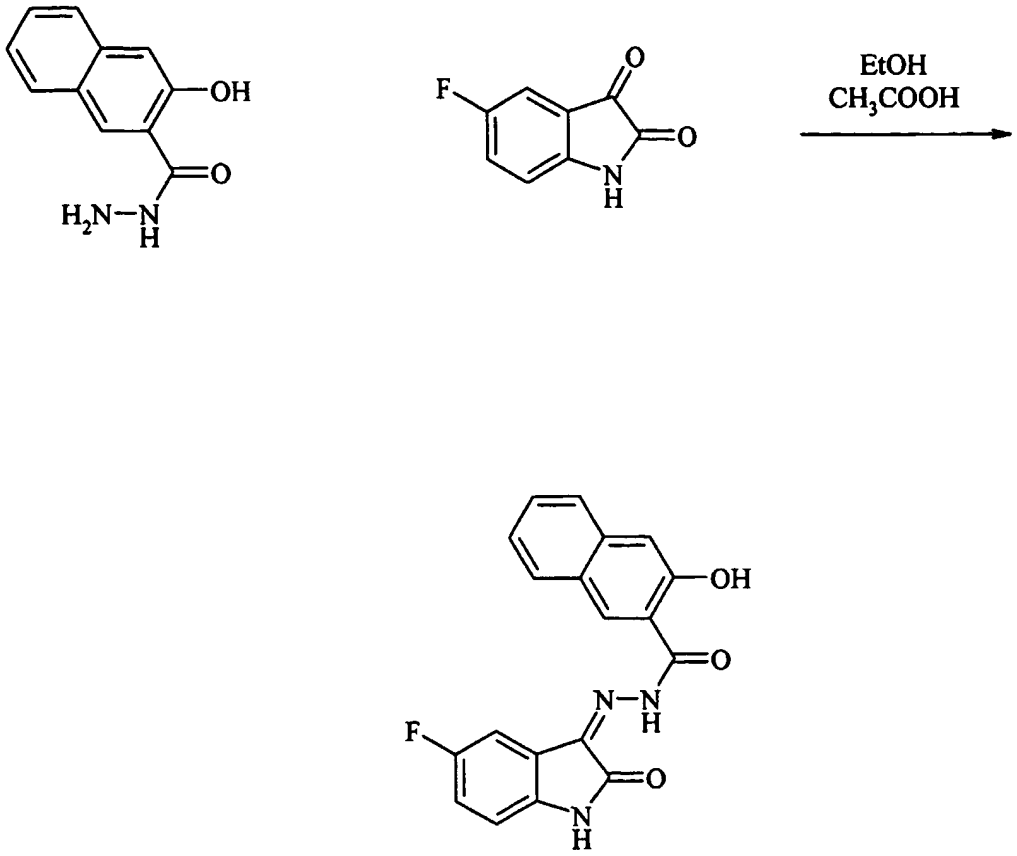
Compound 4

Scheme 2



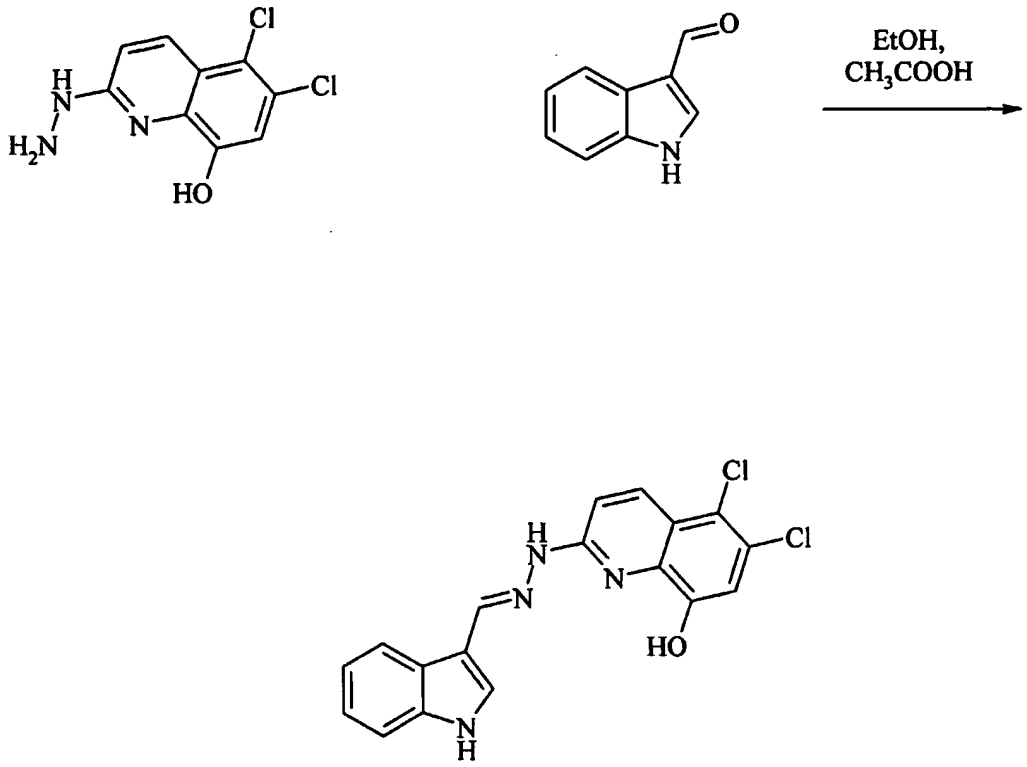
Compound 7

Scheme 3



Compound 8

Scheme 4

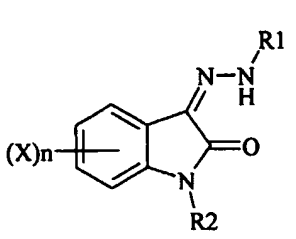


Compound 10

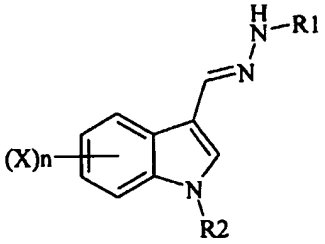
Scheme 5

CLAIMS

1. A pharmaceutical composition for treatment of diseases and disorders caused by or associated with heparanase catalytic activity, said composition comprising a pharmaceutically acceptable carrier and a heparanase inhibitor which is an indole compound of the general Formula I or Formula II:



(I)



(II)

wherein

R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; or heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R2 is hydrogen; C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; said C6-C14 aryl or heteroaryl being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R3 and R4 each independently represents hydrogen, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

or R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

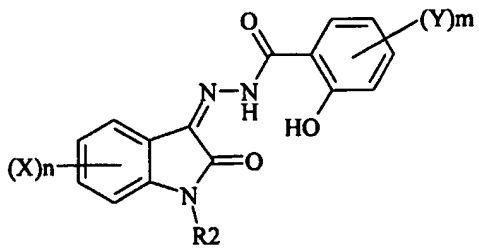
X represents halogen, nitro, -OR3, -SR3, -NR3R4, -SO_3H, –COOR3, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

n is an integer from 0 to 4;

and pharmaceutically acceptable salts thereof.

2. A pharmaceutical composition according to Claim 1 comprising a compound of the general Formula I, wherein R1 is C7-C15 aroyl, preferably benzoyl, substituted by hydroxy at the ortho position and optionally further substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy, and R2, R3, R4, X and n are as defined in Claim 1.

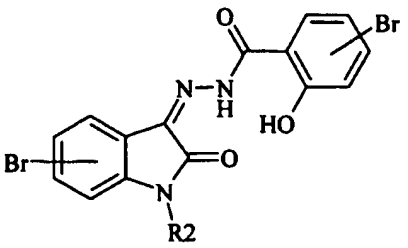
3. A pharmaceutical composition according to Claim 2 comprising a compound of the formula Ia:



(Ia)

wherein Y is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; m is an integer from 0 to 4; and X, R2, R3, R4 and n are as defined in Claim 1.

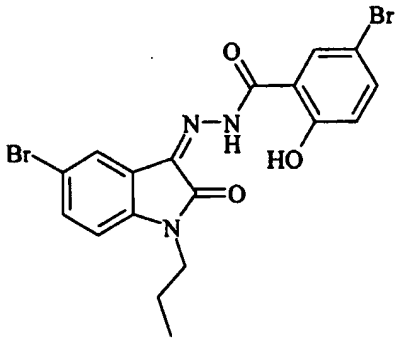
4. A pharmaceutical composition according to Claim 3 comprising a compound of the formula Ib:



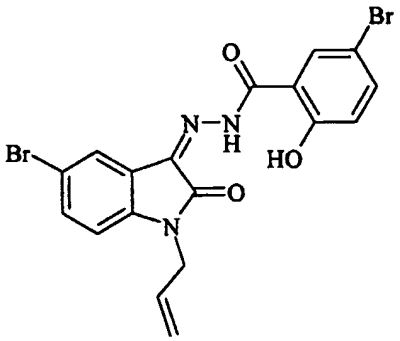
(Ib)

wherein R2 is as defined in Claim 1.

5. A pharmaceutical composition according to Claim 4 comprising the compound herein designated **Compound 1** of the formula:



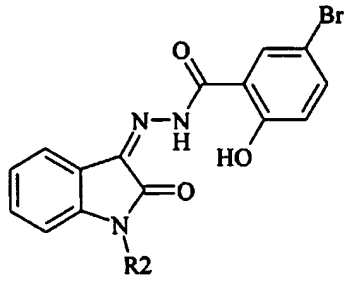
6. A pharmaceutical composition according to Claim 4 comprising the compound herein designated **Compound 2** of the formula:



7. A pharmaceutical composition according to Claim 3 comprising a compound of the formula Ia, wherein Y is halogen, preferably Br at para position to the hydroxy group;

R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; n is 0; and R3 and R4 are as defined in Claim 1.

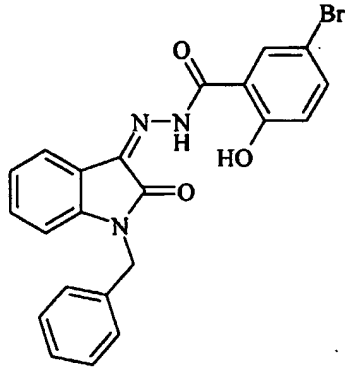
8. A pharmaceutical composition according to Claim 7 comprising a compound of the formula Ib':



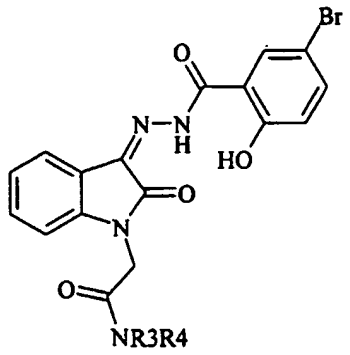
(Ib')

wherein R2 is as defined in Claim 7.

9. A pharmaceutical composition according to Claim 8 comprising the compound herein designated **Compound 3** of the formula:



10. A pharmaceutical composition according to Claim 8 comprising a compound of the formula Ic:

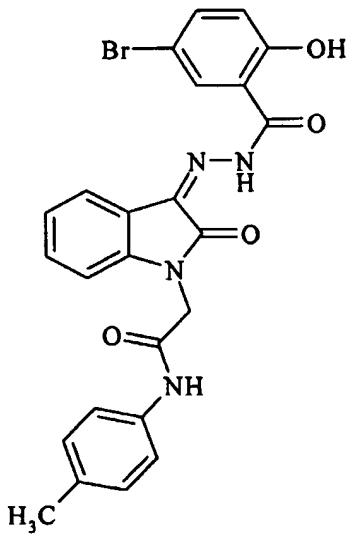


(Ic)

wherein R3 and R4 are as defined in Claim 1.

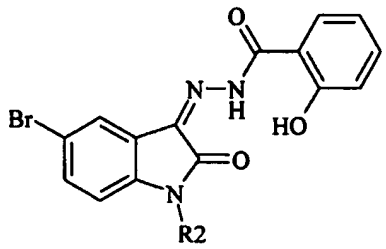
11. A pharmaceutical composition according to Claim 10 comprising a compound of formula Ic, wherein R3 is hydrogen and R4 is C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, $-NH_2$, $-SO_3H$, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, wherein R2 is as defined in Claim 1.

12. A pharmaceutical composition according to Claim 11 comprising the compound herein designated **Compound 4** of the formula:



13. A pharmaceutical composition according to Claim 3 comprising a compound of the formula Ia, wherein X is halogen; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C1-C6 aryl; or C2-C6 alkenyl; m is 0 and n is 1 or 2, and R3 and R4 are as defined in Claim 1.

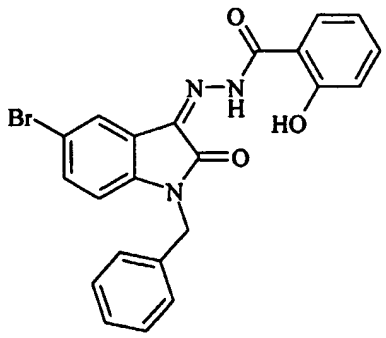
14. A pharmaceutical composition according to Claim 13 comprising the compound of the formula Id:



(Id)

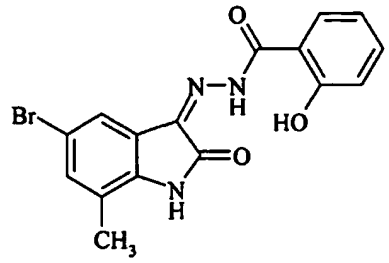
wherein R2 is as defined in Claim 13.

15. A pharmaceutical composition according to Claim 14 comprising a compound herein designated **Compound 5** of the formula:



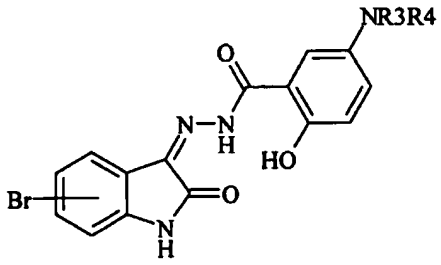
16. A pharmaceutical composition according to Claim 3, comprising a compound of the formula Ia, wherein X is halogen or C1-C6 alkyl; m is 0 and n is 1 or 2; and R2, R3 and R4 are as defined in Claim 1.

17. A pharmaceutical composition according to Claim 16 comprising the compound herein designated **Compound 6** of the formula:



18. A pharmaceutical composition according to Claim 3 comprising a compound of the formula Ia, wherein X is halogen, Y is –NR3R4, n and m are 1, and R2, R3 and R4 are as defined in Claim 1.

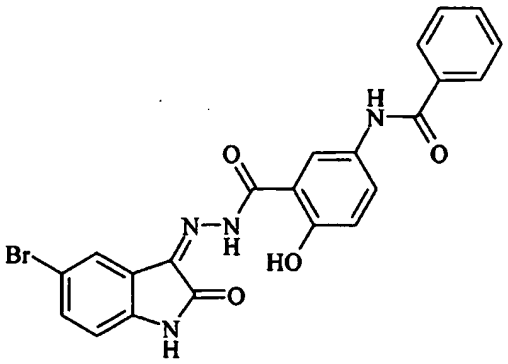
19. A pharmaceutical composition according to Claim 18 comprising a compound of the formula Ie:



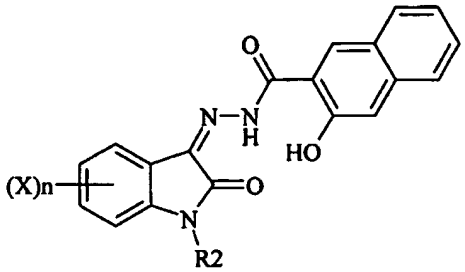
(Ie)

wherein R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, and R2 is as defined in Claim 1.

20. A pharmaceutical composition according to Claim 19 comprising the compound herein designated **Compound 7** of the formula:



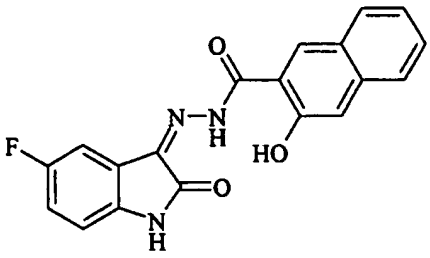
21. A pharmaceutical composition according to Claim 2 comprising a compound of the formula If:



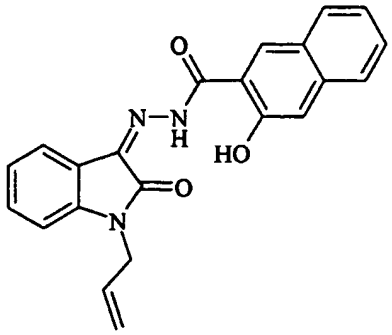
(If)

wherein R2, X and n are as defined in Claim 1.

22. A pharmaceutical composition according to Claim 21 comprising the compound herein designated **Compound 8** of the formula:

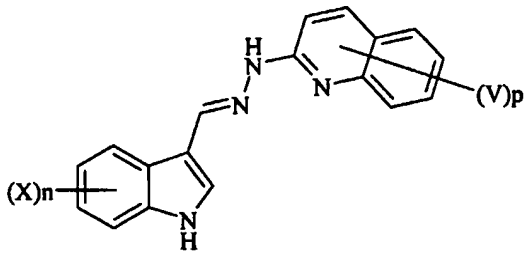


23. A pharmaceutical composition according to Claim 21 comprising the compound herein designated **Compound 9** of the formula:



24. A pharmaceutical composition according to Claim 1 comprising a compound of the general Formula II, wherein R1 is heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; and R2, R3, R4 and n are as defined in Claim 1.

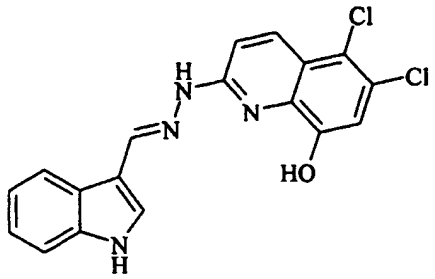
25. A pharmaceutical composition according to Claim 24 comprising a compound of the formula IIa:



(IIa)

wherein V is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; p is an integer from 0 to 6; and X, R3, R4 and n are as defined in Claim 1.

26. A pharmaceutical composition according to Claim 25 comprising the compound herein designated **Compound 10** of the formula:



27. A pharmaceutical composition according to any one of claims 1 to 26 for inhibition of angiogenesis.

28. A pharmaceutical composition according to any one of claims 1 to 26 for treatment or inhibition of a malignant cell proliferative disease or disorder.

29. The pharmaceutical composition according to claim 27 or 28 for the treatment or inhibition of non-solid cancers, e.g hematopoietic malignancies such as all types of leukemia, e.g. acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), mast cell leukemia, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, Burkitt's lymphoma and multiple myeloma.

30. The pharmaceutical composition according to claim 27 or 28 for the treatment or inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea,

retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma.

31. The pharmaceutical composition according to claim 29 or 30 for treating or inhibiting tumor formation, primary tumors, tumor progression or tumor metastasis.

32. A pharmaceutical composition according to any one of claims 1 to 27 for treatment of ophthalmologic disorders such as diabetic retinopathy and macular degeneration, particularly age-related macular degeneration.

33. The pharmaceutical composition according to any one of claims 1 to 26 for inhibiting or treating cell proliferative diseases or disorders such as psoriasis, hypertrophic scars, acne and sclerosis/scleroderma.

34. The pharmaceutical composition according to any one of claims 1 to 26 for inhibiting or treatment of a disease or disorder selected from polyps, multiple exostosis, hereditary exostosis, retrolental fibroplasia, hemangioma, reperfusion of gastric ulcer and arteriovenous malformation.

35. The pharmaceutical composition according to any one of claims 1 to 26 for contraception or for inducing abortion at early stages of pregnancy.

36. The pharmaceutical composition according to any one of claims 1 to 26, for treatment of or amelioration of inflammatory symptoms in any disease, condition or disorder where immune and/or inflammation suppression is beneficial.

37. The pharmaceutical composition according to claim 36, for treatment of or amelioration of inflammatory symptoms in the joints, musculoskeletal and connective tissue disorders.

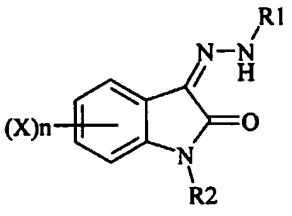
38. The pharmaceutical composition according to claim 36, for treatment of or amelioration of inflammatory symptoms associated with hypersensitivity, allergic

reactions, asthma, atherosclerosis, otitis and other otorhinolaryngological diseases, dermatitis and other skin diseases, posterior and anterior uveitis, conjunctivitis, optic neuritis, scleritis and other immune and/or inflammatory ophthalmic diseases.

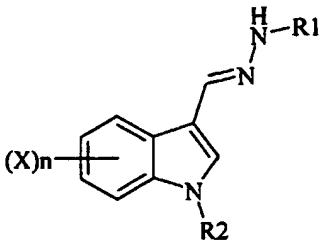
39. The pharmaceutical composition according to any one of claims 1 to 26, for treatment of or amelioration of an autoimmune disease.

40. The pharmaceutical composition according to claim 39, wherein said autoimmune disease is Eaton-Lambert syndrome, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, autoimmune hemolytic anemia (AIHA), hepatitis, insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, plexus disorders e.g. acute brachial neuritis, polyglandular deficiency syndrome, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, thrombocytopenia, thyroiditis e.g. Hashimoto's disease, Sjögren's syndrome, allergic purpura, psoriasis, mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, polyarteritis nodosa, polymyalgia rheumatica, Wegener's granulomatosis, Reiter's syndrome, Behçet's syndrome, ankylosing spondylitis, pemphigus, bullous pemphigoid, dermatitis herpetiformis, Crohn's disease or autism.

41. Use of a heparanase inhibitor being an indole compound of the general Formula I or Formula II:



(I)



(II)

wherein

R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

or heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R2 is hydrogen; C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; said C6-C14 aryl or heteroaryl being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R3 and R4 each independently represents hydrogen, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

or R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

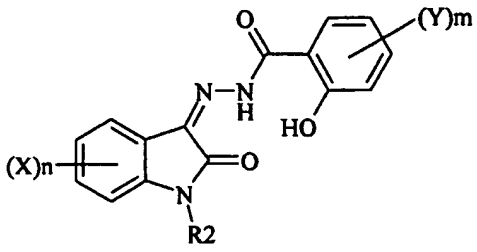
X represents halogen, nitro, -OR3, -SR3, -NR3R4, -SO_3H, –COOR3, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

n is an integer from 0 to 4;

or of a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition that inhibits heparanase activity and is useful in the treatment of a disease or disorder caused by or associated with heparanase catalytic activity.

42. Use according to Claim 41 of a compound of the general Formula I, wherein R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy, and R2, R3, R4, X and n are as defined in Claim 41.

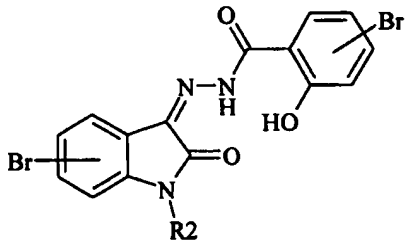
43. Use according to Claim 42 of a compound of the formula Ia:



(Ia)

wherein Y is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; m is an integer from 0 to 4; and X, R2, R3, R4 and n are as defined in Claim 41.

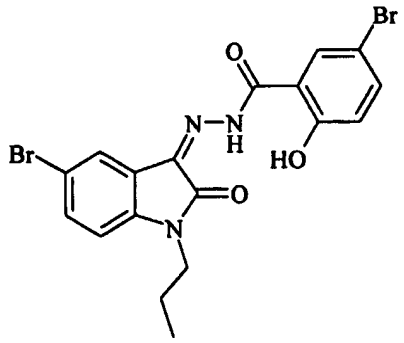
44. Use according to Claim 43 of a compound of the formula Ib:



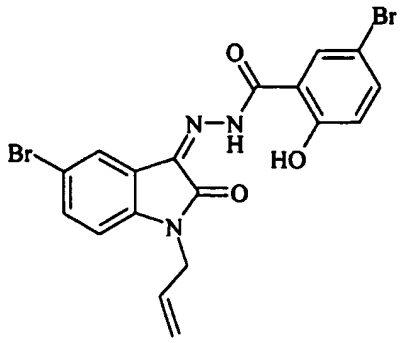
(Ib)

wherein R2 is as defined in Claim 41.

45. Use according to claim 44 of the compound herein designated **Compound 1** of the formula:

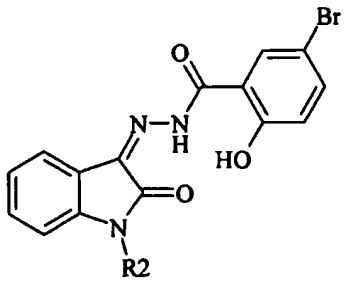


46. Use according to Claim 44 of the compound herein designated **Compound 2** of the formula:



47. Use according to Claim 43 of a compound of the formula Ia, wherein Y is halogen; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; n is 0 and m is an integer from 1 to 4; and R3 and R4 are as defined in Claim 41.

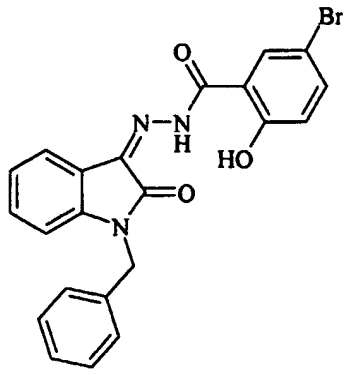
48. Use according to Claim 47 of a compound of the formula Ib':



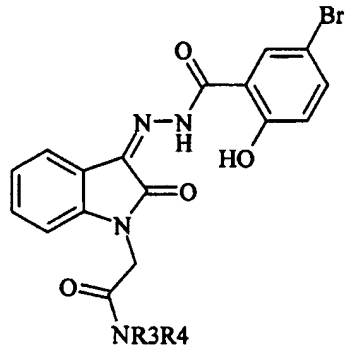
(Ib')

wherein R2 is as defined in Claim 47.

49. Use according to Claim 48 of the compound herein designated **Compound 3** of the formula:



50. Use according to Claim 42 of a compound of the formula Ic:

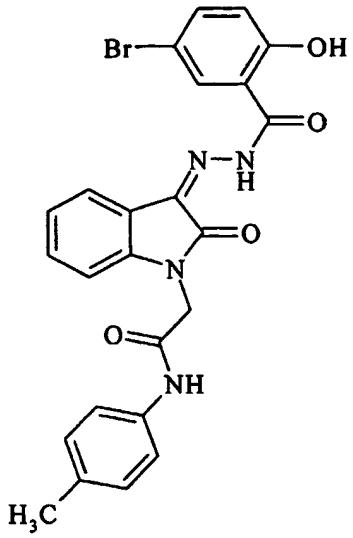


(Ic)

wherein R3 and R4 are as defined in Claim 41.

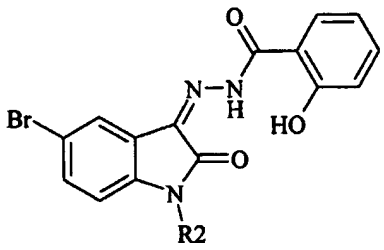
51. Use according to Claim 43 of a compound of formula Ic, wherein R3 is hydrogen and R4 is C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, $-NH_2$, $-SO_3H$, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, wherein R2 is as defined in Claim 41.

52. Use according to Claim 51 of the compound herein designated **Compound 4** of the formula:



53. Use according to Claim 43 of a compound of the formula Ia, wherein X is halogen; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C1-C6 aryl; or C2-C6 alkenyl; m is 0 and n is 1 or 2, and R3 and R4 are as defined in Claim 41.

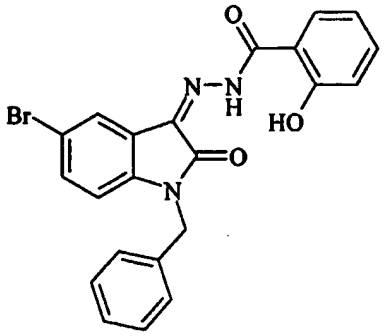
54. Use according to Claim 53 of a compound of the formula Id:



(Id)

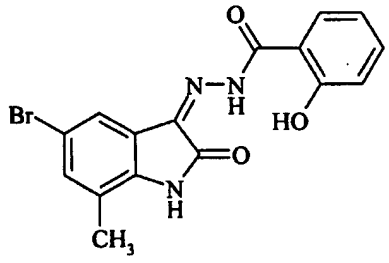
wherein R2 is as defined in Claim 53.

55. Use according to Claim 54 of the compound herein designated **Compound 5** of the formula:



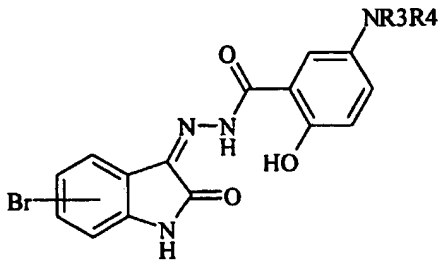
56. Use according to Claim 43 of a compound of the formula Ia, wherein X is halogen or C1-C6 alkyl; m is 0 and n is 1 or 2; and R2, R3 and R4 are as defined in Claim 41.

57. Use according to Claim 56 of the compound herein designated **Compound 6** of the formula:



58. Use according to Claim 43 of a compound of the formula Ia, wherein X is halogen, Y is –NR3R4, n and m are 1, and R2, R3 and R4 are as defined in Claim 41.

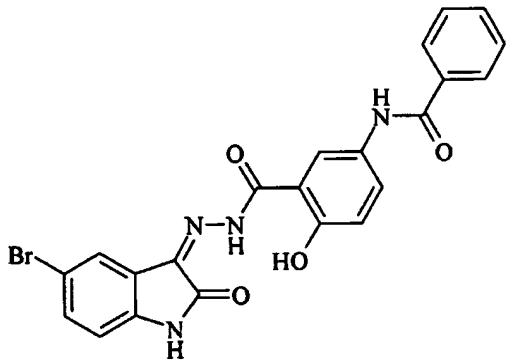
59. Use according to Claim 58 of a compound of the formula Ie:



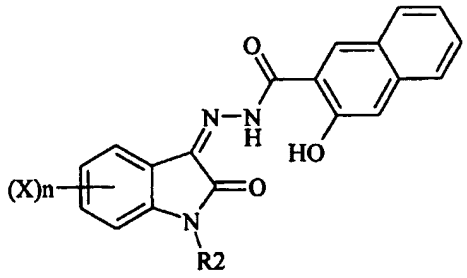
(Ie)

wherein R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, and R2 is as defined in Claim 41.

60. Use according to Claim 59 of the compound herein designated **Compound 7** of the formula:



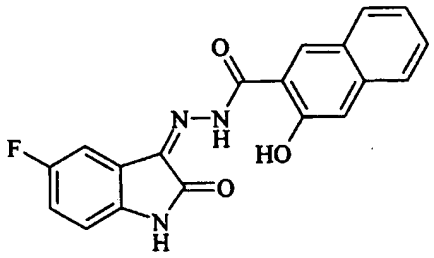
61. Use according to Claim 42 of a compound of the formula If:



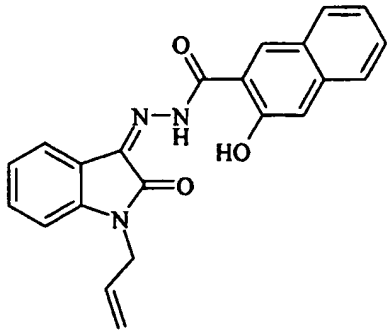
(If)

wherein R2, X and n are as defined in Claim 41.

62. Use according to Claim 61 of the compound herein designated **Compound 8** of the formula:

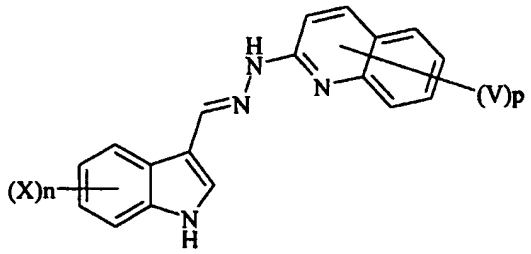


63. Use according to Claim 61 of the compound herein designated **Compound 9** of the formula:



64. Use according to Claim 41 of a compound of the general Formula II, wherein R1 is heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; and R2, R3, R4 and n are as defined in Claim 41.

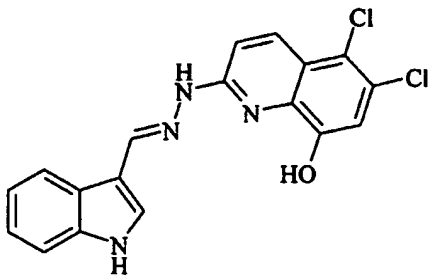
65. Use according to Claim 64 of a compound of the formula IIa:



(IIa)

wherein V is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; p is an integer from 0 to 6; and X, R3, R4 and n are as defined in Claim 41.

66. Use according to Claim 65 of the compound herein designated **Compound 10** of the formula



67. Use according to any one of claims 41 to 66 for the preparation of pharmaceutical composition for inhibition of angiogenesis.

68. Use according to any one of claims 41 to 66 for the preparation of a pharmaceutical composition for treatment or inhibition of a malignant cell proliferative disease or disorder.

69. Use according to claim 67 or 68 for the preparation of a pharmaceutical composition for the treatment or inhibition of non-solid cancers, e.g hematopoietic malignancies such as all types of leukemia, e.g. acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), mast cell leukemia, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, Burkitt's lymphoma and multiple myeloma.

70. Use according to claim 67 or 68 for the preparation of a pharmaceutical composition for the treatment or inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva,

malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma.

71. Use according to claim 69 or 70 for the preparation of a pharmaceutical composition for treating or inhibiting tumor formation, primary tumors, tumor progression or tumor metastasis.

72. Use according to any one of claims 41 to 66 for the preparation of a pharmaceutical composition for treatment of ophthalmologic disorders such as diabetic retinopathy and macular degeneration, particularly age-related macular degeneration.

73. Use according to any one of claims 41 to 66 for the preparation of a pharmaceutical composition for inhibiting or treating cell proliferative diseases or disorders such as psoriasis, hypertrophic scars, acne and sclerosis/scleroderma.

74. Use according to any one of claims 41 to 66 for the preparation of a pharmaceutical composition for inhibition or treatment of a disease or disorder selected from polyps, multiple exostosis, hereditary exostosis, retrolental fibroplasia, hemangioma, reperfusion of gastric ulcer and arteriovenous malformation.

75. Use according to any one of claims 41 to 66 for the preparation of a pharmaceutical composition for contraception or for inducing abortion at early stages of pregnancy.

76. Use according to any one of claims 41 to 66 for the preparation of a pharmaceutical composition for treatment of or amelioration of inflammatory symptoms in any disease, condition or disorder where immune and/or inflammation suppression is beneficial.

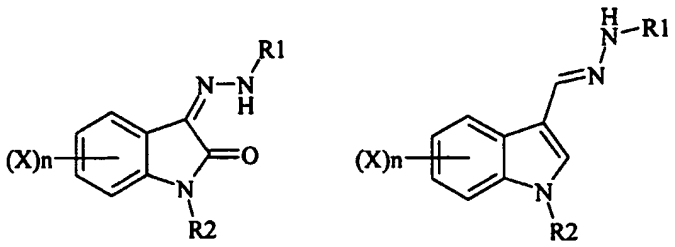
77. Use according to claim 76, wherein said pharmaceutical composition is for treatment of or amelioration of inflammatory symptoms in the joints, musculoskeletal and connective tissue disorders.

78. Use according to claim 76, wherein said pharmaceutical composition is for treatment of or amelioration of inflammatory symptoms associated with hypersensitivity, allergic reactions, asthma, atherosclerosis, otitis and other otorhinolaryngological diseases, dermatitis and other skin diseases, posterior and anterior uveitis, conjunctivitis, optic neuritis, scleritis and other immune and/or inflammatory ophthalmic diseases.

79. Use according to any one of claims 41 to 66 for the preparation of a pharmaceutical composition for treatment of or amelioration of an autoimmune disease.

80. Use according to claim 79 wherein said autoimmune disease is Eaton-Lambert syndrome, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, autoimmune hemolytic anemia (AIHA), hepatitis, insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, plexus disorders e.g. acute brachial neuritis,, polyglandular deficiency syndrome, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, thrombocytopenia, thyroiditis e.g. Hashimoto's disease, Sjögren's syndrome, allergic purpura, psoriasis, mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, polyarteritis nodosa, polymyalgia rheumatica, Wegener's granulomatosis, Reiter's syndrome, Behçet's syndrome, ankylosing spondylitis, pemphigus, bullous pemphigoid, dermatitis herpetiformis, Crohn's disease and autism.

81. A method for treatment of a patient suffering from a disease or disorder caused by or associated with heparanase catalytic activity, which comprises administering to said patient an effective amount of a heparanase inhibitor or a pharmaceutically acceptable salt thereof, said heparanase inhibitor being an indole compound of the general Formula I or Formula II:



(I) (II)

wherein

R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; or heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R2 is hydrogen; C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; said C6-C14 aryl or heteroaryl being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R3 and R4 each independently represents hydrogen, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

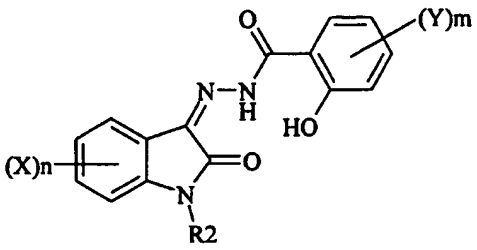
or R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

X represents halogen, nitro, -OR3, -SR3, -NR3R4, -SO_3H, –COOR3, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; and

n is an integer from 0 to 4.

82. A method according to Claim 81 which comprises administering a compound of the general Formula I, wherein R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy, and R2, R3, R4, X and n are as defined in Claim 81.

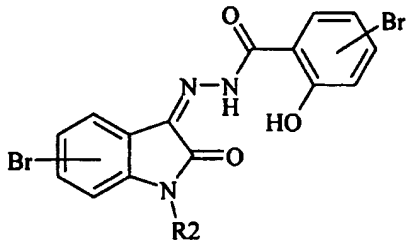
83. A method according to Claim 82 which comprises administering a compound of the formula Ia:



(Ia)

wherein Y is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; m is an integer from 0 to 4; and X, R2, R3, R4 and n are as defined in Claim 81.

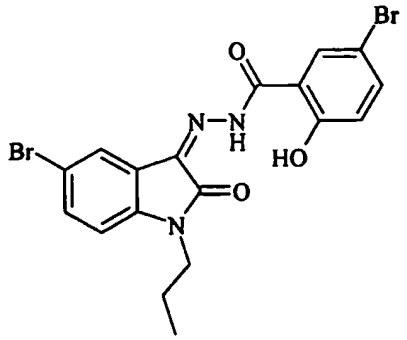
84. A method according to Claim 83, which comprises administering a compound of the formula Ib:



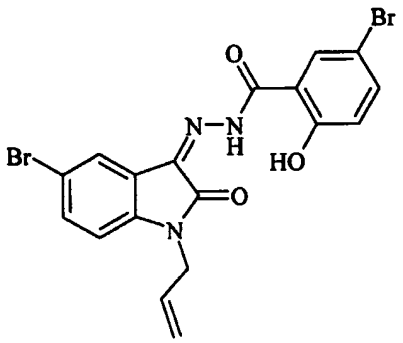
(Ib)

wherein R2 is as defined in Claim 81.

85. A method according to Claim 84 which comprises administering the compound herein designated **Compound 1** of the formula:

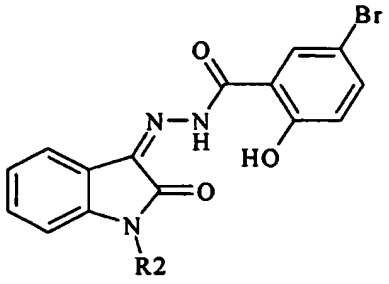


86. A method according to Claim 84 which comprises administering the compound herein designated **Compound 2** of the formula:



87. A method according to Claim 83, which comprises administering a compound of the formula Ia, wherein Y is halogen; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; n is 0 and m is an integer from 1 to 4; and R3 and R4 are as defined in Claim 81.

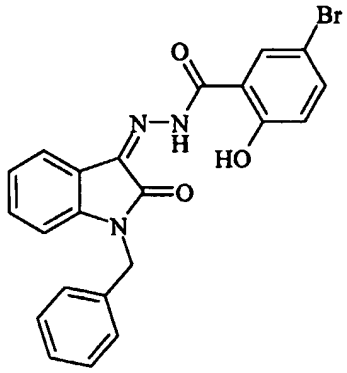
88. A method according to Claim 87 which comprises administering a compound of the formula Ib':



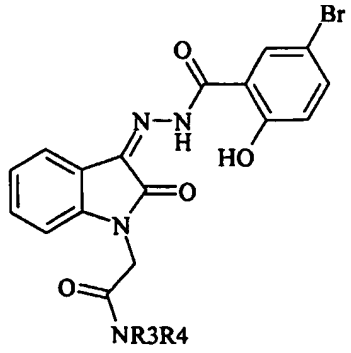
(Ib')

wherein R2 is as defined in Claim 87.

89. A method according to Claim 84 which comprises administering the compound herein designated **Compound 3** of the formula:



90. A method according to Claim 88, which comprises administering a compound of the formula Ic:

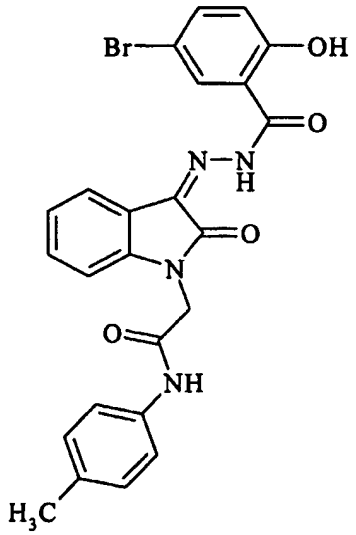


(Ic)

wherein R3 and R4 are as defined in Claim 81.

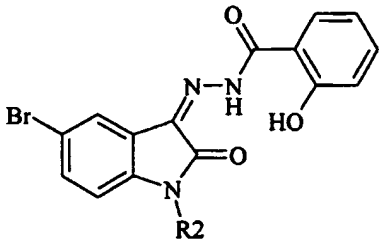
91. A method according to Claim 90, which comprises administering a compound of formula Ic, wherein R3 is hydrogen and R4 is C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, $-NH_2$, $-SO_3H$, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, wherein R2 is as defined in Claim 81.

92. A method according to Claim 90 which comprises administering the compound herein designated **Compound 4** of the formula:



93. A method according to Claim 83, which comprises administering a compound of the formula Ia, wherein X is halogen; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, $-SO_3H$ or C1-C6 aryl; or C2-C6 alkenyl; m is 0 and n is 1 or 2, and R3 and R4 are as defined in Claim 81.

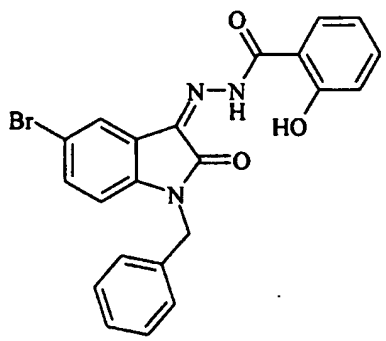
94. A method according to Claim 93, which comprises administering a compound of the formula Id:



(Id)

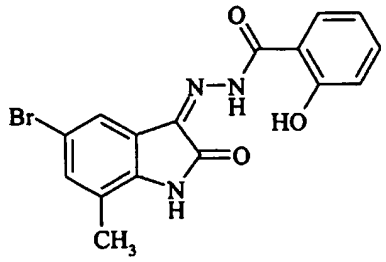
wherein R2 is as defined in Claim 93.

95. A method according to Claim 93 which comprises administering the compound herein designated **Compound 5** of the formula:



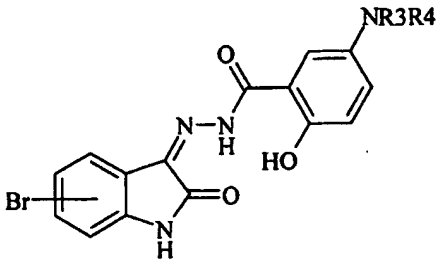
96. A method according to Claim 83, which comprises administering a compound of the formula Ia, wherein X is halogen or C1-C6 alkyl; m is 0 and n is 1 or 2; and R2, R3 and R4 are as defined in Claim 81.

97. A method according to Claim 96 which comprises administering the compound herein designated **Compound 6** of the formula:



98. A method according to Claim 83, which comprises administering a compound of the formula Ia, wherein X is halogen, Y is –NR3R4, n and m are 1, and R2, R3 and R4 are as defined in Claim 81.

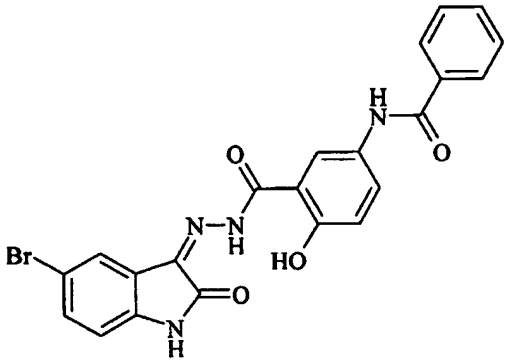
99. A method according to Claim 98 which comprises administering a compound of the formula Ie:



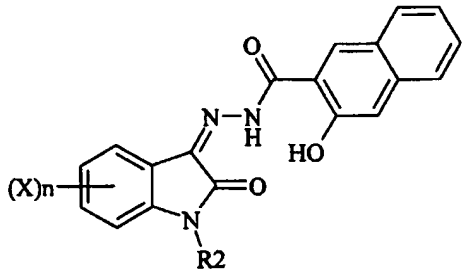
(Ie)

wherein R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, and R2 is as defined in Claim 81.

100. A method according to Claim 99 which comprises administering the compound herein designated **Compound 7** of the formula:



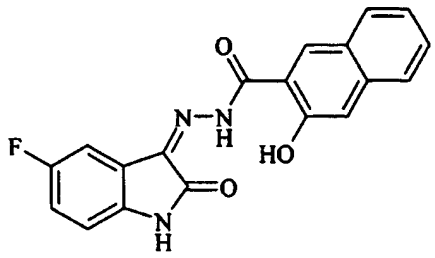
101. A method according to Claim 82, which comprises administering a compound of the formula If:



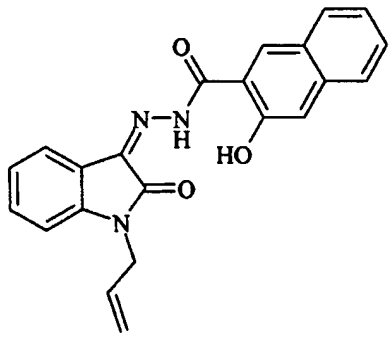
(If)

wherein R2, X and n are as defined in Claim 81.

102. A method according to Claim 101 which comprises administering the compound herein designated **Compound 8** of the formula:

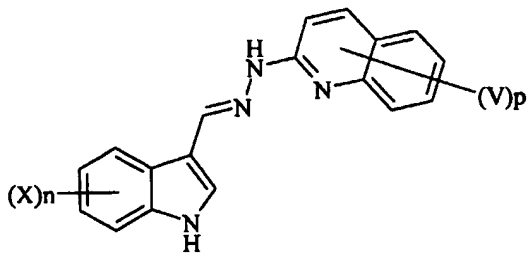


103. A method according to Claim 101 which comprises administering the compound herein designated **Compound 9** of the formula:



104. A method according to Claim 81, which comprises administering a compound of the general Formula II, wherein R1 is heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; and R2, R3, R4 and n are as defined in Claim 81.

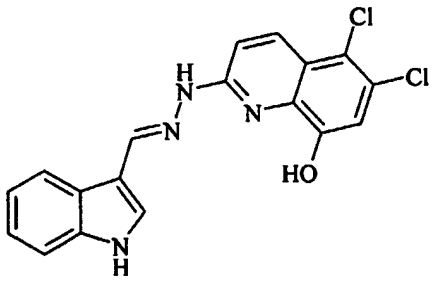
105. A method according to Claim 104 which comprises administering a compound of the formula IIa:



(IIa)

wherein V is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; p is an integer from 0 to 6; and X, R3, R4 and n are as defined in Claim 81.

106. A method according to Claim 105 which comprises administering the compound herein designated **Compound 10** of the formula:



107. A method according to any one of claims 81 to 106 for inhibition of angiogenesis.

108. A method according to any one of claims 81 to 106 for treatment or inhibition of a malignant cell proliferative disease or disorder.

109. A method according to claim 107 or 108 for the treatment or inhibition of a non-solid cancer, e.g a hematopoietic malignancy such as any type of leukemia, e.g. acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), mast cell leukemia, hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphomas, Burkitt's lymphoma and multiple myeloma.

110. A method according to claim 107 or 108 for the treatment or inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of vater, exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri, corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter,

urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma.

111. A method according to claim 109 or 110 for treating or inhibiting tumor formation, primary tumors, tumor progression or tumor metastasis.

112. A method according to any one of claims 81 to 106 for treatment of ophthalmologic disorders such as diabetic retinopathy and macular degeneration, particularly age-related macular degeneration.

113. A method according to any one of claims 81 to 106 for inhibiting or treating cell proliferative diseases or disorders such as psoriasis, hypertrophic scars, acne and sclerosis/scleroderma.

114. A method according to any one of claims 81 to 106 for inhibiting or treatment of a disease or disorder selected from polyps, multiple exostosis, hereditary exostosis, retrolental fibroplasia, hemangioma, reperfusion of gastric ulcer and arteriovenous malformation.

115. A method according to any one of claims 81 to 106 for contraception or for inducing abortion at early stages of pregnancy.

116. A method according to any one of claims 81 to 106 for treatment of or amelioration of inflammatory symptoms in any disease, condition or disorder where immune and/or inflammation suppression is beneficial.

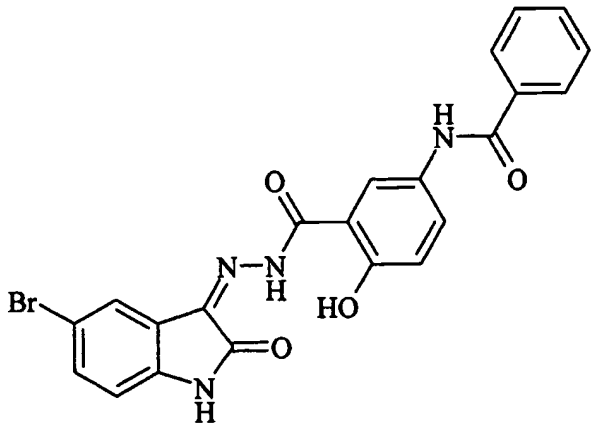
117. A method according to claim 116, for treatment of or amelioration of inflammatory symptoms in the joints, musculoskeletal and connective tissue disorders.

118. A method according to claim 116, for treatment of or amelioration of inflammatory symptoms associated with hypersensitivity, allergic reactions, asthma, atherosclerosis, otitis and other otorhinolaryngological diseases, dermatitis and other skin diseases, posterior and anterior uveitis, conjunctivitis, optic neuritis, scleritis and other immune and/or inflammatory ophthalmic diseases.

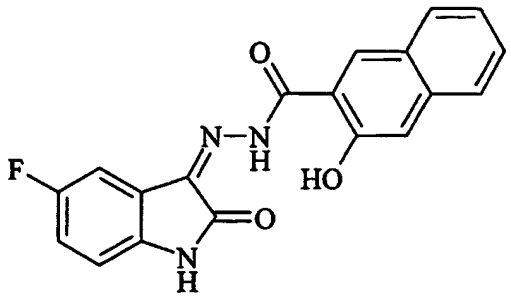
119. A method according to any one of claims 81 to 106 for treatment of or amelioration of an autoimmune disease.

120. A method according to claim 119 wherein said autoimmune disease is Eaton-Lambert syndrome, Goodpasture's syndrome, Grave's disease, Guillain-Barré syndrome, autoimmune hemolytic anemia (AIHA), hepatitis, insulin-dependent diabetes mellitus (IDDM), systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, plexus disorders e.g. acute brachial neuritis, polyglandular deficiency syndrome, primary biliary cirrhosis, rheumatoid arthritis, scleroderma, thrombocytopenia, thyroiditis e.g. Hashimoto's disease, Sjögren's syndrome, allergic purpura, psoriasis, mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, polyarteritis nodosa, polymyalgia rheumatica, Wegener's granulomatosis, Reiter's syndrome, Behçet's syndrome, ankylosing spondylitis, pemphigus, bullous pemphigoid, dermatitis herpetiformis, Crohn's disease or autism.

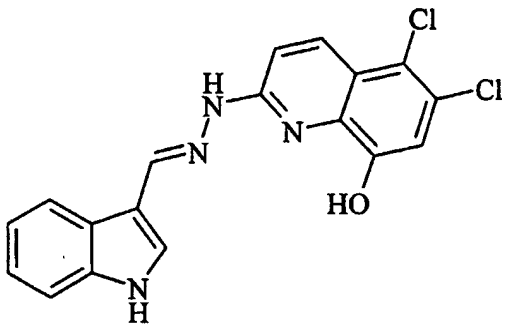
121. The compound herein designated **Compound 7** of the formula:



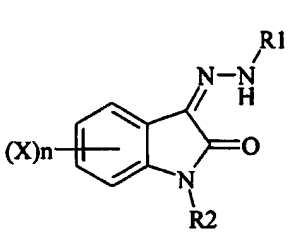
122. The compound herein designated **Compound 8** of the formula:



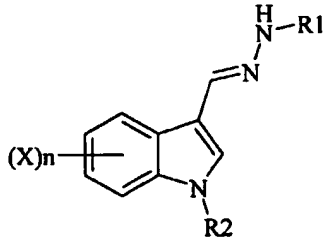
123. The compound herein designated **Compound 10** of the formula:



124. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one indole compound of the general Formula I or Formula II:



(I)



(II)

wherein

R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

or heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R2 is hydrogen; C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; said C6-C14 aryl or heteroaryl being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R3 and R4 each independently represents hydrogen, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

or R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

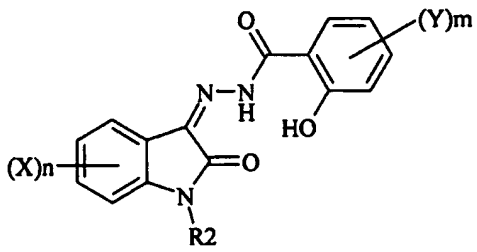
X represents halogen, nitro, -OR3, -SR3, -NR3R4, -SO_3H, –COOR3, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

125. A pharmaceutical composition according to Claim 124 comprising a compound of the general Formula I, wherein R1 is C7-C15 aroyl, preferably benzoyl, substituted by hydroxy at the ortho position and optionally further substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy, and R2, R3, R4, X and n are as defined in Claim 124.

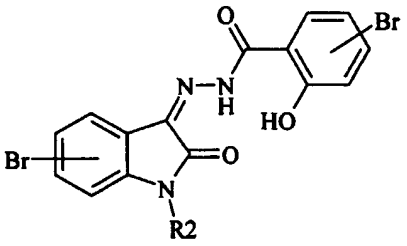
126. A pharmaceutical composition according to Claim 125 comprising a compound of the formula Ia:



(Ia)

wherein Y is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; m is an integer from 0 to 4; and X, R2, R3, R4 and n are as defined in Claim 124.

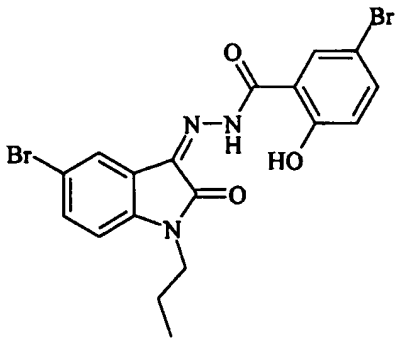
127. A pharmaceutical composition according to Claim 126 comprising a compound of the formula Ib:



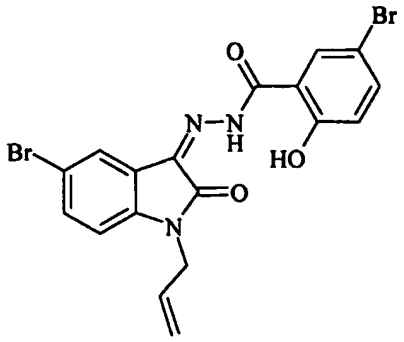
(Ib)

wherein R2 is as defined in Claim 124.

128. A pharmaceutical composition according to Claim 127 comprising the compound herein designated **Compound 1** of the formula:

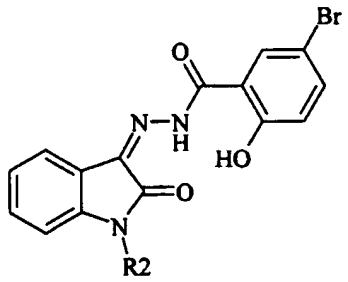


129. A pharmaceutical composition according to Claim 127 comprising the compound herein designated **Compound 2** of the formula:



130. A pharmaceutical composition according to Claim 126 comprising a compound of the formula Ia, wherein Y is halogen, preferably Br at para position to the hydroxy group; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; n is 0; and R3 and R4 are as defined in Claim 124.

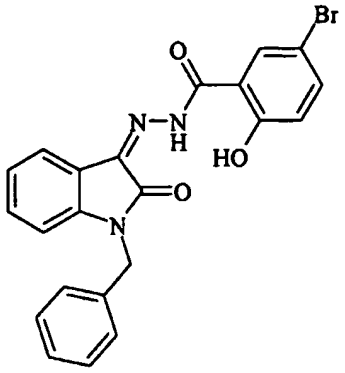
131. A pharmaceutical composition according to Claim 130 comprising a compound of the formula Ib':



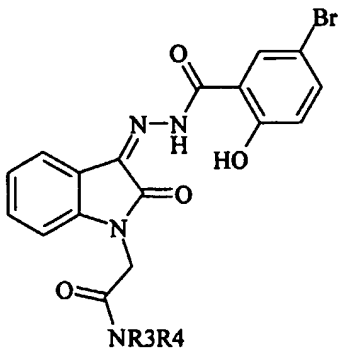
(Ib')

wherein R2 is as defined in Claim 130.

132. A pharmaceutical composition according to Claim 131 comprising the compound herein designated **Compound 3** of the formula:



133. A pharmaceutical composition according to Claim 131 comprising a compound of the formula Ic:

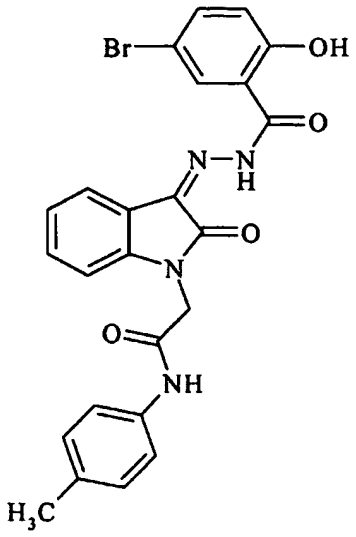


(Ic)

wherein R3 and R4 are as defined in Claim 124.

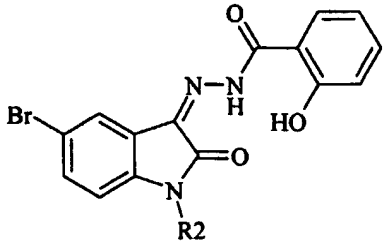
134. A pharmaceutical composition according to Claim 133 comprising a compound of formula Ic, wherein R3 is hydrogen and R4 is C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, $-NH_2$, $-SO_3H$, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, wherein R2 is as defined in Claim 124.

135. A pharmaceutical composition according to Claim 134 comprising the compound herein designated **Compound 4** of the formula:



136. A pharmaceutical composition according to Claim 126 comprising a compound of the formula Ia, wherein X is halogen; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C1-C6 aryl; or C2-C6 alkenyl; m is 0 and n is 1 or 2, and R3 and R4 are as defined in Claim 124.

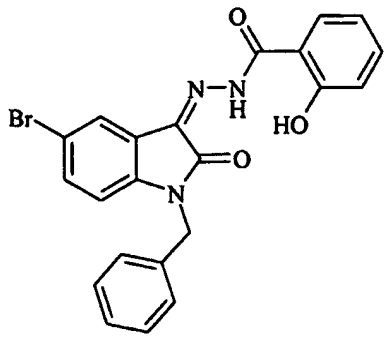
137. A pharmaceutical composition according to Claim 136 comprising the compound of the formula Id:



(Id)

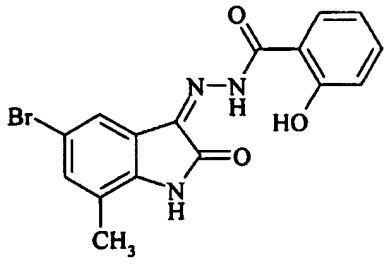
wherein R2 is as defined in Claim 136.

138. A pharmaceutical composition according to Claim 137 comprising a compound herein designated **Compound 5** of the formula:



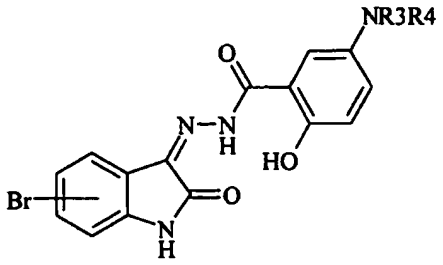
139. A pharmaceutical composition according to Claim 126, comprising a compound of the formula Ia, wherein X is halogen or C1-C6 alkyl; m is 0 and n is 1 or 2; and R2, R3 and R4 are as defined in Claim 124.

140. A pharmaceutical composition according to Claim 139 comprising the compound herein designated **Compound 6** of the formula:



141. A pharmaceutical composition according to Claim 126 comprising a compound of the formula Ia, wherein X is halogen, Y is –NR3R4, n and m are 1, and R2, R3 and R4 are as defined in Claim 124.

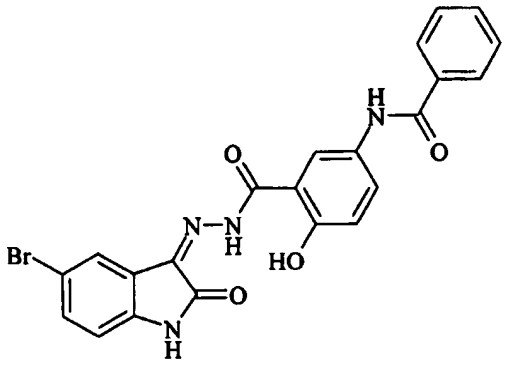
142. A pharmaceutical composition according to Claim 141 comprising a compound of the formula Ie:



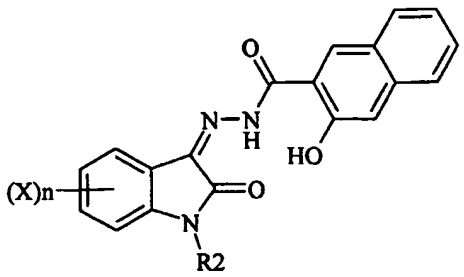
(Ie)

wherein R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, and R2 is as defined in Claim 124.

143. A pharmaceutical composition according to Claim 142 comprising the compound herein designated **Compound 7** of the formula:



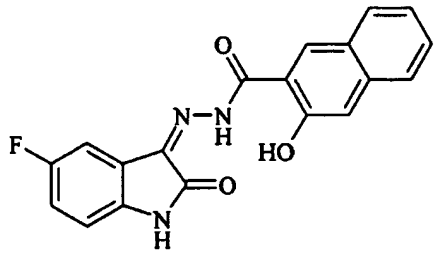
144. A pharmaceutical composition according to Claim 125 comprising a compound of the formula If:



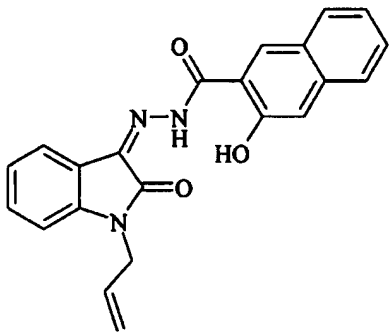
(If)

wherein R2, X and n are as defined in Claim 124.

145. A pharmaceutical composition according to Claim 144 comprising the compound herein designated **Compound 8** of the formula:

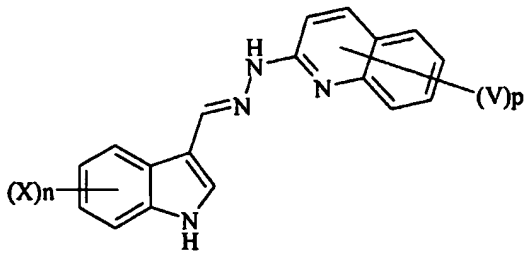


146. A pharmaceutical composition according to Claim 144 comprising the compound herein designated **Compound 9** of the formula:



147. A pharmaceutical composition according to Claim 124 comprising a compound of the general Formula II, wherein R1 is heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; and R2, R3, R4 and n are as defined in Claim 124.

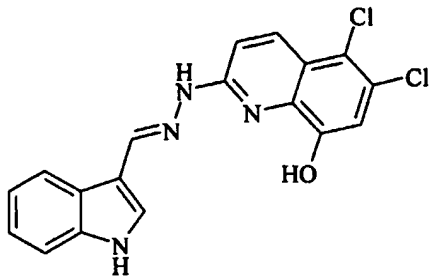
148. A pharmaceutical composition according to Claim 147 comprising a compound of the formula IIa:



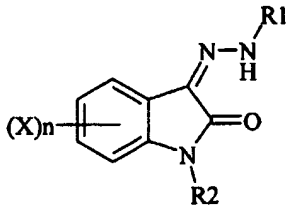
(IIa)

wherein V is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; p is an integer from 0 to 6; and X, R3, R4 and n are as defined in Claim 124.

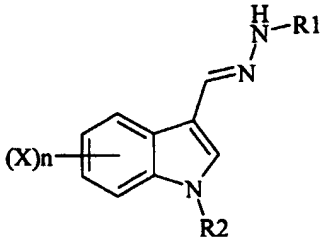
149. A pharmaceutical composition according to Claim 148 comprising the compound herein designated **Compound 10** of the formula:



150. Use of an indole compound of the general Formula I or Formula II:



(I)



(II)

wherein

R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; or heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R2 is hydrogen; C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; said C6-C14 aryl or heteroaryl being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

R3 and R4 each independently represents hydrogen, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

or R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl;

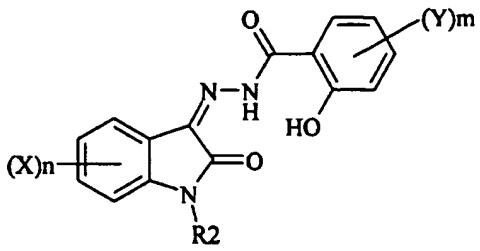
X represents halogen, nitro, -OR3, -SR3, -NR3R4, -SO_3H, –COOR3, C1-C6 alkyl, C2-C6 alkenyl, or C6-C14 aryl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy;

n is an integer from 0 to 4;

or of a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition.

151. Use according to Claim 150 of a compound of the general Formula I, wherein R1 is C7-C15 aroyl optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy, and R2, R3, R4, X and n are as defined in Claim 150.

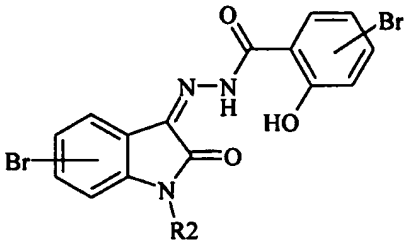
152. Use according to Claim 151 of a compound of the formula Ia:



(Ia)

wherein Y is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; m is an integer from 0 to 4; and X, R2, R3, R4 and n are as defined in Claim 150.

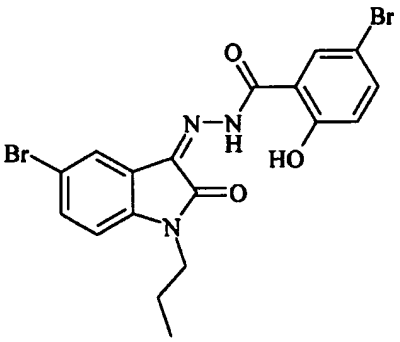
153. Use according to Claim 152 of a compound of the formula Ib:



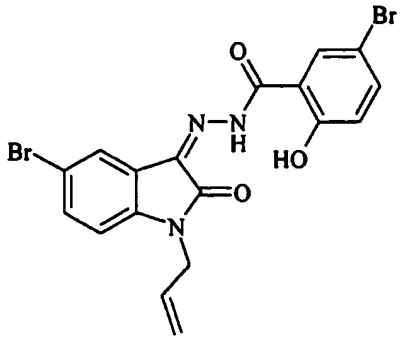
(Ib)

wherein R2 is as defined in Claim 150.

154. Use according to claim 153 of the compound herein designated **Compound 1** of the formula:

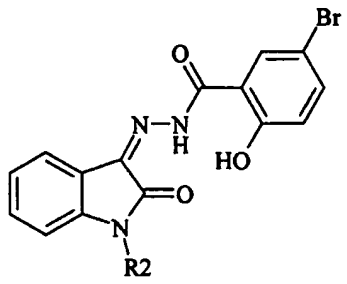


155. Use according to Claim 153 of the compound herein designated **Compound 2** of the formula:



156. Use according to Claim 152 of a compound of the formula Ia, wherein Y is halogen; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C6-C14 aryl; C2-C6 alkenyl; C6-C14 aryl; or heteroaryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S; n is 0 and m is an integer from 1 to 4; and R3 and R4 are as defined in Claim 150.

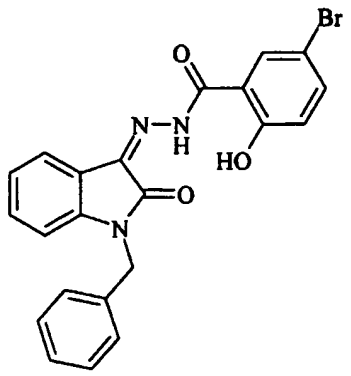
157. Use according to Claim 156 of a compound of the formula Ib':



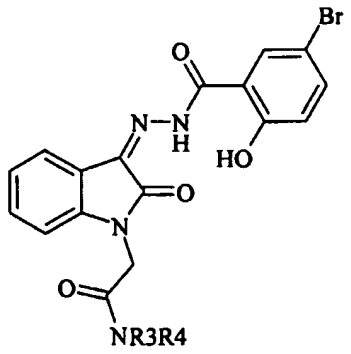
(Ib')

wherein R2 is as defined in Claim 156.

158. Use according to Claim 157 of the compound herein designated **Compound 3** of the formula:



159. Use according to Claim 151 of a compound of the formula Ic:

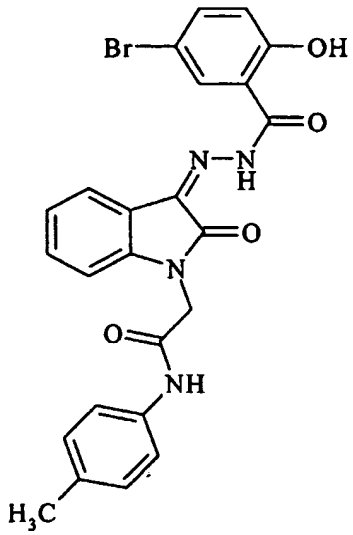


(Ic)

wherein R3 and R4 are as defined in Claim 150.

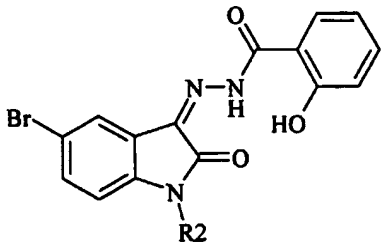
160. Use according to Claim 152 of a compound of formula Ic, wherein R3 is hydrogen and R4 is C6-C14 aryl optionally substituted by halogen, hydroxy, nitro, $-NH_2$, $-SO_3H$, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, wherein R2 is as defined in Claim 150.

161. Use according to Claim 160 of the compound herein designated **Compound 4** of the formula:



162. Use according to Claim 152 of a compound of the formula Ia, wherein X is halogen; R2 is C1-C6 alkyl optionally substituted by halogen, hydroxy, nitro, -NR3R4, -COOR3, -CONR3R4, -SO_3H or C1-C6 aryl; or C2-C6 alkenyl; m is 0 and n is 1 or 2, and R3 and R4 are as defined in Claim 150.

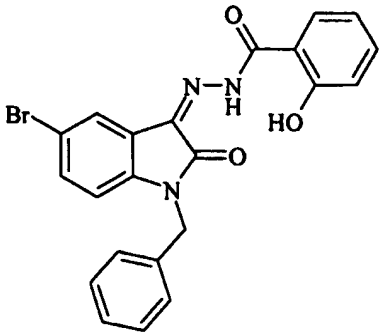
163. Use according to Claim 162 of a compound of the formula Id:



(Id)

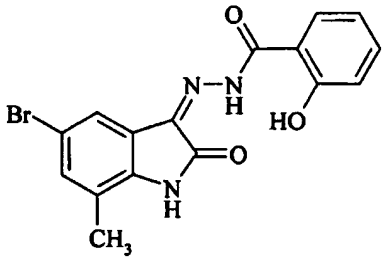
wherein R2 is as defined in Claim 162.

164. Use according to Claim 163 of the compound herein designated **Compound 5** of the formula:



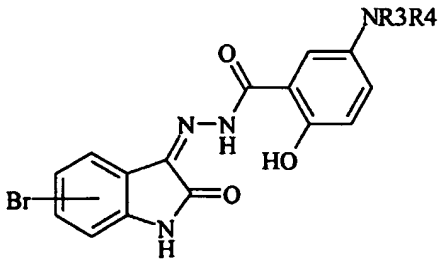
165. Use according to Claim 152 of a compound of the formula Ia, wherein X is halogen or C1-C6 alkyl; m is 0 and n is 1 or 2; and R2, R3 and R4 are as defined in Claim 150.

166. Use according to Claim 165 of the compound herein designated **Compound 6** of the formula:



167. Use according to Claim 152 of a compound of the formula Ia, wherein X is halogen, Y is –NR3R4, n and m are 1, and R2, R3 and R4 are as defined in Claim 150.

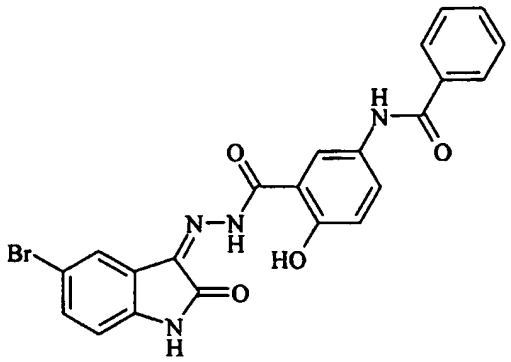
168. Use according to Claim 167 of a compound of the formula Ie:



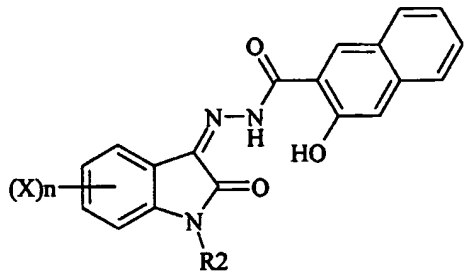
(Ie)

wherein R3 is H and R4 is a C7-C15 aroyl optionally substituted by halogen, hydroxy, nitro, -NH_2, -SO_3H, –COOR2, C1-C6 alkyl, or C2-C6 alkenyl, and R2 is as defined in Claim 150.

169. Use according to Claim 168 of the compound herein designated **Compound 7** of the formula:



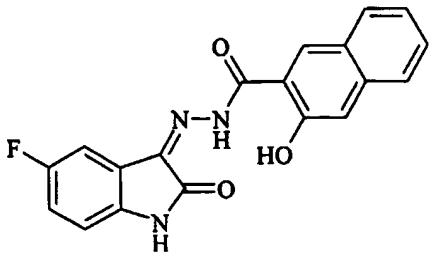
170. Use according to Claim 151 of a compound of the formula If:



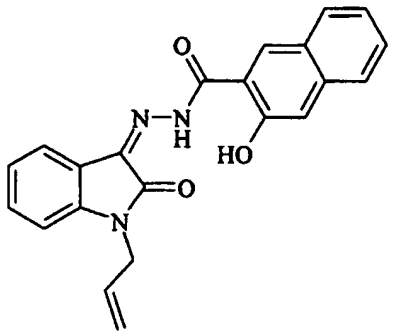
(If)

wherein R2, X and n are as defined in Claim 150.

171. Use according to Claim 170 of the compound herein designated **Compound 8** of the formula:

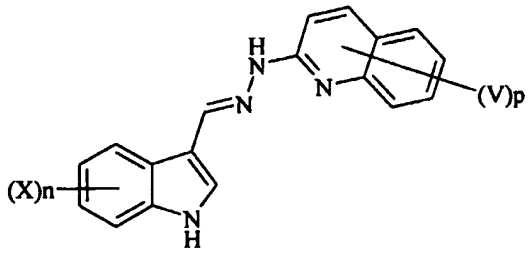


172. Use according to Claim 170 of the compound herein designated **Compound 9** of the formula:



173. Use according to Claim 150 of a compound of the general Formula II, wherein R1 is heteraryl derived from a mono- or poly-cyclic heteroaromatic ring containing one to three heteroatoms selected from N, O and/or S, and being optionally substituted by at least one radical selected from halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; and R2, R3, R4 and n are as defined in Claim 150.

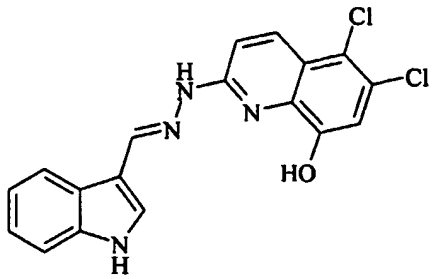
174. Use according to Claim 173 of a compound of the formula IIa:



(IIa)

wherein V is halogen, hydroxy, nitro, -NR3R4, -SO_3H, C1-C6 alkyl, C2-C6 alkenyl, or C1-C6 alkoxy; p is an integer from 0 to 6; and X, R3, R4 and n are as defined in Claim 150.

175. Use according to Claim 174 of the compound herein designated **Compound 10** of the formula:



1/1

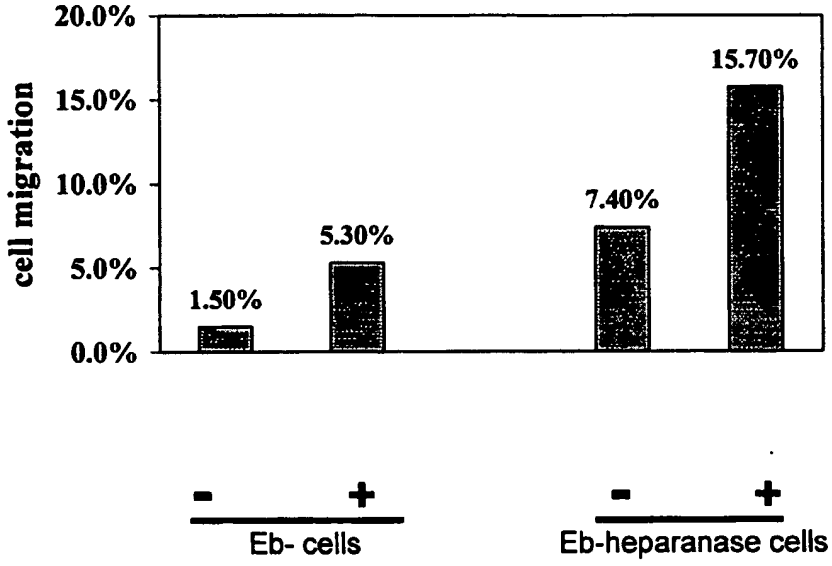


Fig. 1A

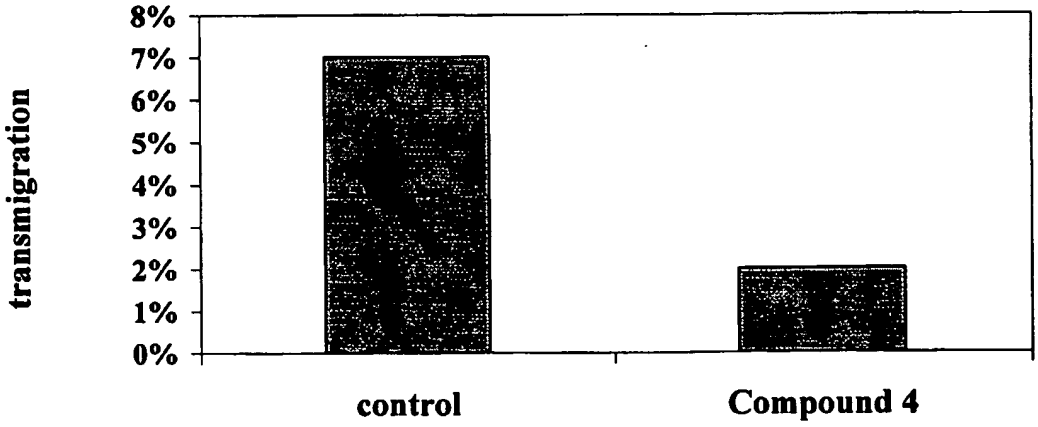


Fig. 1B